Keynes & Aidley's Nerve and Muscle

Fifth edition

This well-established and acclaimed textbook introducing the rapidly growing field of nerve and muscle function has been completely revised and updated. Written with undergraduate students in mind, it begins with the fundamental principles demonstrated by the pioneering electrophysiological experiments on cell excitability. This leads to more challenging material recounting recent discoveries from applying modern biochemical, genetic, physiological and biophysical, experimental and mathematical analysis. The resulting interdisciplinary approach conveys a unified contemporary understanding of nerve, and skeletal, cardiac and smooth muscle, function at the molecular, cellular and systems levels. Emphasis on important strategic experiments throughout clarifies the basis for our current scientific views, highlights the excitement and challenge of biomedical discovery, and suggests directions for future advance. These fundamental ideas are then translated into discussions of related disease conditions and their clinical management. Now including colour illustrations, it is an invaluable text for students of physiology, neuroscience, cell biology and biophysics.

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Fifth edition

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To friends and teachers: *In Memoriam Absentium, in Salutem Praesentium:*

Charles Michel and Morrin Acheson: The Queen's College, Oxford.

David Weatherall and John Ledingham: Nuffield Department of Medicine, University of Oxford.

Richard Adrian: Physiological Laboratory, University of Cambridge.

For at the first she will walk with him by crooked ways, and bring fear and dread upon him, and torment him with her discipline, until she may trust his soul, and try him by her laws. Then will she return the straight way unto him, and comfort him, and shew him her secrets.
Ecclesiasticus 4:17-18: King James Version (KJV)

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Preface

Initiation of movement, whether voluntary action by skeletal muscle or contraction of cardiac or smooth muscle, is the clearest observable physiological manifestation of animal life. It inevitably involves activation of contractile tissue initiated or modulated by altered activity in its nerve supply or signalling by its chemical modulators. An appreciation of structure and function in both nerve and muscle, and of the functional relationships between them, is fundamental to our physiological understanding. These processes, and their regulation and abnormalities, now also assume increasing applicability to the understanding and clinical management of disease processes.

This book introduces this important biological area in a form suitable for students taking university courses in physiology, cell biology or medicine. It gives a straightforward account of the fundamentals of this subject, whilst including some of the strategic classical and recent experimental evidence underpinning our current understanding.

Besides providing rewritten and reorganised chapters, this fifth edition covers major advances in this important and rapidly developing area of study. It includes contributions from recent molecular structural insights, opportunities arising from genetic manipulation, novel single-cell and multi-channel electrophysiological and optical recording techniques, and physical and mathematical analysis. It extends our appreciation of the implications of these molecular and cellular findings to the systems level. Many of these developments were prompted by their applicability to clinical medicine that itself has both inspired and become increasingly amenable to physiological analysis. They have led to major new insights from the resulting exciting and important discoveries concerning the molecules involved in electrical activity, activation of skeletal muscle and the function of cardiac and smooth muscle. This edition increases emphasis on new findings in excitation–contraction coupling, cardiac electrophysiology and arrhythmogenesis, and the cellular physiology of smooth muscle.

Nevertheless, in the spirit of previous editions, the earlier as well as introductory sections of the subsequent chapters in this revision first emphasise fundamental physiological principles prior to narrating more challenging recent material. In the course of this revision, I am particularly grateful to my current collaborators, Drs. Antony Jackson, Kamalan Jeevaratnam, Ming Lei, Hugh Matthews, James Fraser and Samantha Salvage, as well as undergraduate and postgraduate students in my college and laboratory, for stimulating pedagogical insights and continued scientific dialogue. I am also grateful for a visiting professorship generously awarded by the University of Surrey in the course of this revision.

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Prof. William F. Gilly, Hopkins Marine Station, CA, USA (Figure 5.4). American Physiological Society: *American Journal of Physiology* (Plate 19); *Physiological Reviews* (Plates 21 and 22, Figure 5.3). American Society for Biochemistry and Molecular Biology: *Journal of Biological Chemistry* (Plate 1); Company of Biologists Ltd.: *Journal of Cell Science* (Figure 14.7). Elsevier BV: *Advances in Surgery* (Figure 1.8); *Brain Research Reviews* (Figure 8.13); *Cardiovascular Research* (Plate 20); *Cell* (Plate 2); *Mechanisms of Ageing and Development* (Plate 18); *Neuroscience* (Figure 7.1); *Progress in Biophysics and Molecular Biology* (Plate 5). Federation of European Biochemical Societies (FEBS) Press: *FEBS Letters* (Plate 3). Frontiers Media SA: *Frontiers in Physiology* (Plates 11 and 16). John Wiley & Sons Inc: *Acta Physiologica* (Plates 20 and 24; Figure 14.6); *Biological Reviews of the Cambridge Philosophical Society* (Figure 8.13); *Clinical and Experimental Pharmacology and Physiology* (Plate 14); *Experimental Physiology* (Plate 24); *Journal of Anatomy* (Plate 4, Figure 10.7); *Journal of Cardiovascular Electrophysiology* (Figure 14.8); *Journal of Physiology* (Plate 5, 7, 10 and 17, and Figures 3.7, 3.13, 5.4, 7.3, 7.4, 7.7–7.9, 10.1–10.5, 10.10, 11.1, 11.3, 11.4, 11.12, 11.14, 12.16, 13.8, 14.2, 15.3, 15.5–15.7 and 15.9); *Protein Science* (Plates 8 and 9). *Proceedings of the National Academy of Sciences USA (PNAS)* (Plate 2). Rockefeller University Press: *Biophysical Journal* (Figure 10.6); *Journal of General Physiology* (Plate 7; Figures 10.12, 10.13). Society for Neuroscience: *Journal of Neuroscience* (Figure 7.1). Royal Society (Great Britain): *Open Biology* (Plate 18); *Bibliographical Memoirs of the Royal Society* (Figure 11.2). Springer-Nature: *Pflugers Archiv-European Journal of Physiology* (Plate 14, Figure 12.17); *Scientific Reports* (Figure 11.16).

Abbreviations used in the text

Notes:

(1) Units provided to give indication of unit dimensions are those frequently encountered in the physiological literature.
(2) Ion channel α-subunits, their currents and their encoding genes are summarised in Plates 6 and 13.

a	constant in the Hill equation
A	actin
αAR	α-adrenergic receptor
A-band	anisotropic band
AC	adenylyl cyclase
ACh	acetylcholine
AChR	acetylcholine receptor
A-curve	action potential restitution: dependence of APD on BCL
ADP	adenosine diphosphate
AF	atrial fibrillation
AgCl	silver chloride
α_h	Hodgkin–Huxley, *h*-variable, forward rate constant (/sec)
α_m	Hodgkin–Huxley, *m*-variable, forward rate constant (/sec)
α_n	Hodgkin–Huxley, *n*-variable, forward rate constant (/sec)
-AM	acetomethoxy (ester)
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate
Ano1	gene encoding anoctamin-1 (Ca^{2+}-activated Cl^- channel)
2-APB	2-aminoethoxydiphenylborate (IP_3R blocker)
APD	action potential duration (ms)
APD_{90}	action potential duration to 90% full repolarisation (ms)
ARVC	arrhythmogenic right ventricular cardiomyopathy
ATP	adenosine triphosphate
ATP/ADP	ATP/ADP ratio
AV	atrioventricular
aVF	electrocardiogram recording between left leg and combined two remaining leads
aVL	electrocardiogram recording between left arm and combined two remaining leads
AVN	atrioventricular node

aVR	electrocardiogram recording between right arm and combined two remaining leads
Aα	peripheral nerve fibre subtype; conduction velocity ~100 m/s
Aβ	peripheral nerve fibre subtype; conduction velocity ~60 m/s
Aγ	peripheral nerve fibre subtype; conduction velocity ~40 m/s
b	constant in the Hill equation
B	peripheral nerve fibre subtype; conduction velocity ~10 m/s
Ba^{2+}	barium ion
BAPTA	1,2-bis(o-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid tetrakis-acetoxymethyl ester
βAR	β-adrenergic receptor
BCL	basic cycle length (ms)
BDNF	brain-derived neurotrophic factor
β_h	Hodgkin–Huxley, *h*-variable, backward rate constant (/sec)
β_m	Hodgkin–Huxley, *m*-variable, backward rate constant (/sec)
β_n	Hodgkin–Huxley, *n*-variable, backward rate constant (/sec)
BK	large-conductance, Ca^{2+}-activated K^+ channel (maxiK)
BrS	Brugada syndrome
C	peripheral nerve fibre subtype; conduction velocity ~2 m/s
CACNA1C-G402S	L-type Ca^{2+} channel mutation involving the junction between DI/S6 and the I-II loop of Cav1.2
CACNA1C-G406R	L-type Ca2+ channel mutation involving the junction between DI/S6 and the I-II loop of Cav1.2
Cacna1g	gene encoding T-type $Ca_V3.2$ channel
Cacna1h	gene encoding T-type $Ca_V3.2$ channel
$[Ca^{2+}]_i$.	intracellular free Ca^{2+} concentration (mmol/L)
$[Ca^{2+}]_o$	extracellular Ca^{2+} concentration (mmol/L)
CaM	Ca^{2+}/calmodulin
CaMK	CaM-dependent kinase
CaMKII	calmodulin kinase II
cAMP	cyclic 3',5',-adenosine monophosphate
CASQ	calsequestrin
CASQ2	calsequestrin type 2, cardiac isoform
Cav1.1	L-type Ca^{2+} channel type 1, skeletal muscle isoform
Cav1.2	L-type Ca^{2+} channel type 2, cardiac muscle isoform
$Ca_V3.2$	T-type Ca^{2+} channel

-CH_3	methyl-
CH_3–NH_3^+	methylamine ion
Cl^-	chloride ion
$[Cl^-]_i$	intracellular Cl^- concentration (mMol/L)
$[Cl^-]_o$	extracellular Cl^- concentration (mMol/L)
ClC-1	Cl^- conducting channel
CLIC2	chloride intracellular channel protein 2
c_m	capacitance of unit length of fibre (μF/cm)
C_m	specific membrane capacitance of unit surface area (μF/cm^2)
CN	calcineurin
CN^-	cyanide ion
CPVT	catecholaminergic polymorphic ventricular tachycardia
8-CPT	8-(4-chlorophenylthio)adenosine-3',5'-cyclic monophosphate (Epac activator)
Cr	creatine
CrP	creatine phosphate
cryo-EM	cryo-electronmicroscope
Cs^+	caesium ion
CSD	cortical spreading depression
c_T	tubular membrane capacitance (μF/cm)
CT	crista terminalis
Cx	connexin
Cx40	connexin type 40
Cx43	connexin type 43
d	membrane thickness (nm)
D600	methoxyverapamil
DAD	delayed after-depolarisation
DAG	diacylglycerol
ΔAPD	transmural action potential duration gradient (ms)
ΔAPD_{90}	transmural repolarisation gradient in action potential duration to 90% recovery (ms)
DHPR	dihydropyridine receptor
DHPR1	dihyropyridine receptor type 1, skeletal muscle isoform, Cav1.1
DHPR2	dihyropyridine receptor type 2, cardiac muscle isoform, Cav1.2
DI	diastolic interval (ms)
di-4-ANEPPS	3-(4-{2-[6-(dibutylamino)naphthalen-2-yl]ethenyl}pyridinium-1-yl)propane-1-sulfonate
di-8-ANEPPS	3-[4-[(*E*)-2-[6-(dioctylamino)naphthalen-2-yl]ethenyl]pyridin-1-ium-1-yl]propane-1-sulfonate
DI_{crit}	critical DI where the restitution A-curve shows unity slope (ms)
DI	voltage-gated ion channel domain I
DII	voltage-gated ion channel domain II

DIII	voltage-gated ion channel domain III
DIV	voltage-gated ion channel domain IV
D-line	action potential restitution (consequence for DI of varying APD)
DNP	2,4-dinitrophenol
ΔV_c	cell volume change (μL)
dV/dt	action potential upstroke velocity (mV/ms)
$(dV/dt)_{max}$	maximum action potential upstroke velocity (mV/ms)
dV/dx	voltage drop with respect to distance along the intracellular space (mV/cm)
$\partial V/\partial x$	voltage gradient along length of fibre (mV/cm)
e	electron charge (C)
E	membrane potential (mV)
$\hat{E}$	transmembrane electric field (V/m)
ε	permittivity (F/m)
ε_r	dielectric constant
EAD	early after-depolarisation
ECG	electrocardiogram
EF-hand	Ca^{2+} binding protein motif
EGTA	ethylene glycol-bis(β-aminoethyl ether)-*N*,*N*,*N*′,*N*′-tetraacetic acid
E_K	K^+ Nernst equilibrium potential (mV)
ELC	essential myosin light chain
E_m	membrane potential (mV)
EMF	electromotive force (mV)
E_{Na}	Na^+ Nernst equilibrium potential (mV)
Epac	exchange protein directly activated by cAMP
EPP	end-plate potential
EPSC	excitatory postsynaptic current
EPSP	excitatory postsynaptic potential
ERP	effective refractory period (ms)
F	Faraday constant (C/mol)
ξ	fraction of the total voltage drop V across the membrane
FDNB	1-fluoro-2,4-dinitrobenzene
FK506	tacrolimus; fujimycin
FKBP	FK506 binding protein
FKBP12	FK506 binding protein type 12
G-protein	guanosine triphosphate binding protein
$G_1(V)$	energy of channel resting state (J/mol)
$G_2(V)$	energy of channel activated state (J/mol)
$G_a(V)$	energy of transition state (J/mol)
GABA	gamma-amino butyric acid
g_{Ca}	membrane Ca^{2+} conductance (mS/cm^2)
GDP	guanosine diphosphate
g_f	membrane HCN channel conductance (mS/cm^2)
GFP	green fluorescent protein
GH	growth hormone

G_i	adenylyl cyclase inhibitory G-protein
G_{i2}	adenylyl cyclase inhibitory G-protein
$G_{i/o}$	adenylyl cyclase inhibitory G-protein
g_K	membrane K^+ conductance (mS/cm^2)
$\bar{g}_K$	maximum K^+ conductance (mS/cm^2)
g_{leak}	membrane leak conductance (mS/cm^2)
g_{Na}	membrane Na^+ conductance (mS/cm^2)
$\bar{g}_{Na}$	maximum Na^+ conductance (mS/cm^2)
G_q	phospholipase C activating G-protein
Group I	myelinated sensory fibre subtype, diameter 20 to 12 μm
Group II	myelinated sensory fibre subtype, diameter 12 to 4 μm
Group III	myelinated sensory fibre subtype, diameter <4 μm
G_s	adenylyl cyclase stimulatory G-protein
GTP	guanosine triphosphate
G_α	GTP binding subunit of trimeric G-protein
$G\beta\gamma$	βγ component of trimeric G-protein
h	Hodgkin–Huxley, Na^+ conductance inactivation variable
H^+	hydrogen ion
HCN	hyperpolarisation-induced cyclic nucleotide-activated channel
HCS	hydrophobic constriction site, Na^+ channel
HEK293	Human embryonic kidney 293
HgCl	mercuric chloride
HMM	heavy meromyosin
5-HT	5-hydroxytryptamine
^{1}H-NMR	proton nuclear magnetic resonance
^{2}H-NMR	deuterium nuclear magnetic resonance
H-zone	Heller zone (German 'heller': brighter).
θ	action potential propagation velocity (m/s)
I	current
$I(V,t)$	charge movement (if normalised to background membrane capacitance: μA/μF)
I_0	current electrode; three-microelectrode voltage clamp (mA)
$I_0(t)$	current delivered to control voltage at V_1; three-microelectrode voltage clamp (mA)
i_a	axial current flow along the length, x, of a fibre (mA)
$i_a(t)$	axial intracellular current; three-microelectrode voltage clamp (mA)
I-band	isotropic band
I_{Ca}	Ca^{2+} current
I_{CaL}	voltage-gated L-type Ca^{2+} current carried by Cav1.1 or Cav1.2
I_{CaT}	voltage-gated T-type Ca^{2+} current carried by Cav3.1 or Cav3.2

I_{cat}	cationic current
ICC	interstitial cells of Cajal
ICC-CM	interstitial cells of Cajal within gastrointestinal circular muscle
ICC-DMP	interstitial cells of Cajal within deep muscular plexus between small intestinal inner and outer circular muscle sublayers
ICC-LM	interstitial cells of Cajal within gastrointestinal longitudinal muscle
ICC-MP or ICC MY	interstitial cells of Cajal between the circular and longitudinal muscle layers
ICC-SM	interstitial cells of Cajal between submucosa and circular muscle
ICC-SMP	submucosal interstitial cells of Cajal
ICC-SS	interstitial cells of Cajal within the subserosal connective tissue space
$I_{Cl(Ca)}$	Ca^{2+}-activated Cl^- current
I_{crac}	Ca^{2+}-release-activated (capacitative) current
I_{dr}	delayed rectifying K^+ current
IFMT	inactivation amino acid sequence, Na^+ channel
IGF-1	insulin-like growth factor 1
I_i	ionic current (mA/cm^2)
I_K	K^+ current
i_K	K^+ current per unit length of fibre (mA/cm)
$I_{K(ACh)}$	acetylcholine-gated K^+ current carried by Kir3.1
I_{K1}	inward ('anomalous') rectifying K^+ current carried by Kir2.1, Kir2.2 and Kir2.3
I_{K2p}	2-pore domain K^+ leak current carried by TWIK1 or TASK1
I_{KATP}	adenosine triphosphate (ATP)-sensitive K^+ current carried by Kir6.2
I_{KCa}	Ca^{2+} activated K^+ current carried by KCa1.1
I_{Kp}	two-pore domain K^+ channel mediated K^+ current carried by TWIK1 or TASK1
I_{Kr}	voltage-gated rapidly activating outward K^+ current carried by Kv11.1
I_{Ks}	voltage-gated slowly activating outward K^+ current carried by Kv7.1
I_{Kur}	voltage-gated ultra-rapidly activating atrial outward K^+ current carried by Kv1.5
I_m	membrane current (mA/cm^2)
i_m	transmembrane current per unit length of fibre (mA/cm^2)
$i_m(t)$	membrane current in the fibre segment extending a distance $3l/2$ from end; three-microelectrode voltage clamp (mA/cm); l, electrode distancing.
I_{maxK}	Ca^{2+}-activated K^+ current

I_{Na}	voltage-gated Na^+ current carried by Nav1.1, Nav1.4, Nav1.5
i_{Na}	Na^+ current per unit length of fibre (mA/cm)
I_{NaL}	late Na^+ current
I_{NCX}	Na^+–Ca^{2+} exchanger current
IP_3	inositol *tris*phosphate
IP_3R	inositol 1,4,5-*tris*phosphate receptor
IPSP	inhibitory postsynaptic potential
IQ domain	isoleucine-glutamine Ca^{2+}/calmodulin binding domain
I_{sac}	stretch-activated current
I_{ti}	transient inward current
I_{to}	early transient outward K^+ current
$I_{to,f}$	voltage-gated fast transient outward current carried by $K_v4.2$, Kv4.3
$I_{to,s}$	voltage-gated slow transient outward K^+ current carried by $K_v1,4$
IVC	inferior venacava
JNK	c-Jun N-terminal kinase
k	Boltzmann constant (J/K)
k	steepness factor, Boltzmann equation (mV)
K^+	potassium ion
$[K^+]_i$	intracellular K^+ concentration (mmol/L)
$[K^+]_o$	extracellular K^+ concentration (mmol/L)
K_{ATP}	ATP-sensitive K^+ channel
KChIP2	K^+ channel interacting protein 2
KCNH2	encoding gene for protein carrying I_{Kr}
KCNQ1	encoding gene for protein carrying I_{Ks}
K_{dr}	delayed rectifier K^+ channel
Kir	inwardly rectifying K^+ channel
Kir1.x, Kir4.x, Kir5.x, Kir7.x	inwardly rectifying K^+ channel variants
Kir2.1, Kir2.2, Kir2.3	K^+ channels carrying I_{K1}
Kir2.x	persistently active inwardly rectifying K^+ channel
Kir3.x	G-protein-receptor-coupled inwardly rectifying K^+ channel
Kir6.2	inward rectifying K^+ channel carrying I_{KATP}
Kir6.x	ATP- sensitive inwardly rectifying K^+ channel
KN-93	N-[2-[N-(4-chlorocinnamyl)-*N*-methylaminomethyl]phenyl]-*N*-(2-hydroxyethyl)-4-methoxybenzenesulfonamide (CaMK II inhibitor)
Kv4.2	K^+ channel, carrying $I_{to,f}$
Kv4.3	K^+ channel, carrying $I_{to,f}$
L	channel number density (channels/μm^2)
Λ	action potential wavelength (mm)
λ	dynamic space constant (mm)

$\lambda(\infty)$	steady-state space constant (mm)
Λ'	action potential wavelength (mm)
Λ_0'	action potential resting wavelength (mm)
$[(\text{lactate})^-]_i$	intracellular lactate ion concentration (mmol/L)
$[(\text{lactate})^-]_o$	extracellular lactate ion concentration (mmol/L)
Lead I	electrocardiogram recording between right and left arm
Lead II	electrocardiogram recording between right arm and left leg
Lead III	electrocardiogram recording between left arm and left leg
LMM	light meromyosin
LQTS	long QT syndrome
LQTS1	long QT syndrome, related to *KCNQ1*-mediated I_{Ks}
LQTS2	long QT syndrome, related to *KCNH2*-mediated I_{Kr}
LQTS3	long QT syndrome type 3 related to *SCN5A*-mediated I_{Na}
LQTS8	long QT syndrome type 8 related to *CACNA1c*-mediated I_{CaL} (Timothy syndrome)
LTD	long-term depression
LTP	long-term potentiation
LV	left ventricle
m	Hodgkin–Huxley, Na^+ conductance activation variable
M	myosin
m	quantal content (mean number of quanta released during an EPP)
M_2	muscarinic receptor type 2
M_3	muscarinic receptor type 3
MAP	monophasic action potential
maxiK	large-conductance, Ca^{2+}-activated K^+ channel (BK)
Mdg	muscular dysgenic
MEPP	miniature end-plate potential
$[Mg^{2+}]_o$	extracellular Mg^{2+} concentration (mmol/L)
mGluR	metabotropic glutamate receptor
Mkk4	mitogen-activated protein kinase kinase 4
Mkk4-acko	conditional *Mkk4* knockout
Mkk4-f/f	*Mkk4* control
MLC	myosin light chain
MLCK	myosin light-chain kinase
M-line	Mittelscheibe line (German: 'Mittel': middle; 'scheibe': disc)
Mn^{2+}	manganese ion
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid

n	Hodgkin–Huxley, K^+ conductance activation variable
N	membrane density of a specified channel or transporter
N2B	cardiac-specific titin element
NA	noradrenaline
Na^+	sodium ion
$[Na^+]_i$	intracellular Na^+ concentration (mmol/L)
$[Na^+]_o$	extracellular Na^+ concentration (mmol/L)
NAD^+	oxidized nicotinamide adenine dinucleotide
NADH	reduced nicotinamide adenine dinucleotide
Nav1.1	α-subunit voltage-dependent Na^+ channel, neuronal isoform
$Na_v1.1$, $Na_v1.2$, $Na_v1.3$, $Na_v1.6$	central nervous system α-subunit voltage-dependent Na^+ channel isoforms
$Na_v1.4$	skeletal muscle α-subunit voltage-dependent Na^+ channel isoform
$Na_v1.5$	cardiac muscle α-subunit voltage-dependent Na^+ channel isoform
$Na_v1.7$, $Na_v1.8$, and $Na_v1.9$	peripheral nervous system α-subunit voltage-dependent Na^+ channel isoforms
NCX	Na^+–Ca^{2+} exchanger
NFAT	nuclear factor of activated T cells
$-NH_2$	amino-
NH_2–NH_3^+	hydrazine
NK_1	neurokinin receptor type 1
NK_3	neurokinin receptor type 3
NKCC1	Na^+-K^+-Cl^- cotransporter type 1
NMDA	*N*–methyl-D-aspartate
nNOS	neuronal nitric oxide synthase
NO	nitric oxide
-OH	hydroxyl-
OH–NH_3^+	hydroxylamine
P	force exerted by the muscle in the Hill equation (N)
P_0	isometric tension in the Hill equation (N)
P1	voltage-gated ion channel p-loop helix 1
P2	voltage-gated ion channel p-loop helix 2
P2XR	ionotropic P2X purinergic receptor
P2YR	metabotropic purinergic receptor
Pak1	p21 activated kinase-1
Pak1-/-	murine p21 activated kinase-1 knockout
Pak1-cko	murine p21 activated kinase-1 conditional knockout
P_{Cl}	membrane permeability to Cl^- (m/s)
PEVK	domains rich in proline (P), glutamate (E), valine (V), and lysine (K)
PGC-1α	peroxisome proliferator-activated receptor-γ coactivator-1α

PGC-1β	peroxisome proliferator-activated receptor-γ coactivator-1β
Pgc-1β$^{-/-}$	murine PGC-1β knockout
pH	negative logarithm to base 10 of [H^+]
Phase 0	cardiac action potential rapid depolarisation phase
Phase 1	cardiac action potential initial brief rapid repolarisation phase
Phase 2	cardiac action potential plateau phase
Phase 3	cardiac action potential terminal repolarisation phase
Phase 4	cardiac action potential electrical diastole
pH_i	logarithm to base 10 of intracellular [H^+]
PIP_2	phosphatidylinositol 4,5-*bis*phosphate
P_K	membrane permeability to K^+ (m/s)
P_k	probability of an EPP containing *k* quanta
pK_a	negative logarithm of dissociation constant
PKA	phosphokinase A
PKC	phosphokinase C
P_{Lac-}	membrane permeability to lactate ion (m/s)
P_{LacH}	membrane permeability to lactate acid (un-ionised) (m/s)
PLC	phospholipase C
PLN	phospholamban
PM	voltage-gated ion channel pore module
PMCA	sarcolemmal Ca^{2+}-ATPase
P_{Na}	membrane permeability to Na^+ (m/s)
PP1	protein phosphatase isoform 1
PP2A	protein phosphatase isoform 2
PPA1	protein phosphatase 1
[Pr^{z-}]	protein concentration (mmol/L)
P-wave	electrocardiogram recording, initial atrial depolarisation-related wave
<q>	microscopic charge movement (if normalised to background membrane capacitance: nC/μF)
Q(V, t)	charge movement (if normalised to background membrane capacitance: nC/μF)
$Q(V,\infty)$	steady state charge (if normalised to background membrane capacitance: nC/μF)
$Q_0(V)$	lipid bilayer charge (if normalised to background membrane capacitance: nC/μF)
Q_{max}	maximum charge (if normalised to background membrane capacitance: nC/μF)
qPCR	quantitative reverse transcriptase polymerase chain reaction
QRS-complex	major ventricular-related ECG deflection
R	universal gas constant (J/(K mol))
R_a	cytoplasmic resistivity (Ω cm)

r_a	intracellular resistance of unit fibre length (kΩ/cm)
r_a	intracellular resistance of unit length (kΩ.cm)
RA	right atrium
r_{ac}	tubular access resistance (kΩ cm)
RH237	(*N*-(4-sulfobutyl)-4-(6-(4-(dibutylamino)phenyl) hexatrienyl)pyridinium [styryl membrane voltage indicator]
Rhod-2	1-[2-amino-5-(3-dimethylamino-6-dimethyl-ammonio-9-xanthenyl)phenoxy-2-(2-amino-5-methylphenoxy)-ethane-*N*,*N*,*N*′,*N*′-tetraaacetic acid (BAPTA-derived Ca^{2+}-sensitive dye)
R_K	membrane resistance attributable to K^+ conductance (kΩ cm^2)
r_L	tubular luminal resistance (kΩ/cm)
RLC	regulatory myosin light chain
R_{leak}	membrane resistance attributable to leak conductance (kΩ cm^2)
r_m	resistance of unit length of fibre (kΩ cm)
R_m	specific membrane resistance (kΩ cm^2)
r_m	surface membrane resistance of unit length of fibre (kΩ cm)
R_{Na}	membrane resistance attributable to Na^+ conductance (kΩ cm^2)
RNA	ribonucleic acid
r_o	extracellular fluid resistance of unit length of nerve fibre (kΩ/cm)
ROCC	receptor-operated cation channel
ROS	reactive oxygen species
R_{patch}	resistance of membrane within the patch (MΩ); loose patch electrode recording
R_{pip}	loose patch clamp electrode resistance (MΩ); loose patch electrode recording
R_{seal}	seal resistance between loose patch electrode and external membrane surface (MΩ); loose patch electrode recording
r_T	tubular membrane resistance (kΩ/cm)
RV	right ventricle
RVOT	right ventricular outflow tract
RyR1	ryanodine receptor type 1, skeletal muscle isoform
RyR2	ryanodine receptor type 2, cardiac muscle isoform
RyR2-P2328S	RyR2 mutation exemplar
$RyR2^{S/+}$	murine heterozygotic *RyR2*-P2328S mutant
$RyR2^{S/S}$	murine homozygotic *RyR2*-P2328S mutant
RyR3	ryanodine receptor type 3, neuronal isoform
S1	myosin subfragment 2

S1	pacing stimulus
S1-S6	transmembrane segments in voltage-gated ion channel domains
S2	extrasystolic stimulus
S2	myosin subfragment 2
SAC	mechanosensitive, stretch-activated, channel
SAN	sino-atrial node
sarcK_{ATP}	sarcolemmal ATP-sensitive K^+ channel
SCF	stem cell factor
Scn5a+/–	heterozygotic Nav1.5 deficient genotype
Scn5a+/ΔKPQ	gain of function cardiac Na^+ channel genotype
Scn5a-1798insD	gain of function cardiac Na^+ channel genotype
SEM	standard error of the mean
SEP	atrial septum
SERCA	sarcoplasmic reticular Ca^{2+} ATPase
SERCA1	sarcoplasmic reticular Ca^{2+}-ATPase type 1, skeletal muscle isoform
SERCA2	sarcoplasmic reticular Ca^{2+}-ATPase type 2, cardiac muscle isoform
SF	ion channel selectivity filter
Slc12a2	gene encoding Na^+-K^+-Cl^- cotransporter type 1
SOCC	store-operated Ca^{2+} channel
SR	sarcoplasmic reticulum
Sr^{2+}	strontium ion
STD	spontaneous transient depolarization events/ unitary potentials
STIC	spontaneous transient inward current
SVC	superior vena cava
T	absolute temperature (K)
t	time (ms)
T–	transverse
τ	time constant (ms)
TdP	torsades de pointes (French: 'twisting of the peaks')
TGF-β_1	transforming growth factor β type 1
TM	tropomyosin
Tris	*tris*-hydroxyaminomethane
TRP	transient receptor potential channel
TRPC1	transient receptor potential channel protein type 1
TRPC3	transient receptor potential channel protein type 3
TRPC6	transient receptor potential channel protein type 6
TTCC	T-type Ca^{2+} channels
T-tubule	transverse tubule
TTX	tetrodotoxin
T-wave	electrocardiogram recording, ventricular-repolarisation-related wave

V	membrane voltage (mV)
V	velocity of shortening in the Hill equation (cm/s)
V	voltage (V)
$V(t)$	membrane voltage at time t (mV)
$V(x)$	membrane voltage at position x (mV)
$V(x, t)$	membrane voltage as a function of x and t (mV)
V^*	membrane voltage at which energies of G_1 and G_2 are equal (mV)
V1–V6	electrocardiogram recording: chest leads 1–6.
V_c	cell volume (μL)
VE	ventricular ectopic
VERP	ventricular ERP (ms)
VF	ventricular fibrillation
VIP	vasoactive intestinal polypeptide
VIP_1	vasoactive intestinal peptide type 1
V_{pip}	voltage at the back end of the pipette (mV); loose patch electrode recording
V_{rest}	external voltage of patched membrane (mV); loose patch electrode recording
VSM	voltage-sensing module, voltage-gated ion channel
VT	ventricular tachycardia
WT	wild type
x	position along length of a nerve (mm)
z	charge valency
Z-line	Zwischenscheibe line (German: 'Zwischen': spacer; 'scheibe': disk)
z_x	effective valency