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Review

The propagation speeds of calcium action potentials are remarkably invariant

Lionel F. Jaffe *

Marine Biological Laboratory, 7 MBL Street, Woods Hole, MA 02543, USA

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Abstract

This paper critically compiles all published cases of established or putative calcium action potentials (or ultrafast calcium waves) where their speeds are known and are not limited by intercellular delays. The 127 cases include data from neurons or nerve nets within systems that range from cnidaria, ctenophores, molluscs, crustaceans, worms, echinoderms and tunicates up to mammalian brains; from muscle cells within organisms that range from *Beröe*, *Cestum*, moths, a crab, molluscs, a tunicate, frogs, chick embryos and turtles up to mammalian hearts; from epithelia in cnidaria and tunicates; even from a dinoflagellate and an insectivorous plant as well as reconstituted heart strands. They reveal a restriction to values of about 10–40 cm/sec at 20 degrees C and comparable restrictions at other temperatures. Moreover – unlike the speeds of sodium action potentials – the speeds of calcium ones are unrelated to cell diameter, at least over the available range of about 0.1 to 30 microns. Why do calcium action potentials have such fixed propagation speeds? Perhaps evolution has driven them to be the fastest waves of calcium influx which avoid subsurface poisoning.

Keywords: Calcium waves; Cardiac; Cnidaria; Heart; Ultrafast

1. Introduction

Calcium waves fall into four natural classes based upon their speeds at 20 °C (Fig. 1). They were discovered in 1978 as the intense calcium waves or tsunamis that are propagated through activating medaka fish eggs (Gilkey et al., 1978). Such fertilization waves are now known to belong to a large class of so-called *fast* calcium waves: Ones which underlie and drive highly diverse phenomena from egg activation to the brain injury waves which cause migraine attacks, which move at 10–30 microns/sec in fully active systems at 20 °C and are propagated by a reaction diffusion mechanism in which diffusing calcium ions are the only propagator (Jaffe,1993; Jaffe and Créton, 1998; Hadjikani et al., 2001).

A second, well established class of calcium waves are the *slow* ones which drive phenomena from cell cleavage to neural induction, move at 0.1 to 1 microns/sec at 20 °C and seem to be mechanically propagated. (Jaffe and Créton, 1998). A third, tentative class of calcium waves are the *ultraslow* ones which seem to underlie diverse developmental phenomena including the progress of the morphogenetic furrow in developing Drosophila eye discs and the extension of the DNA replication band in developing ciliates and generally move at 10 to 60 nanometers/sec (Jaffe, 1999). Here we focus upon calcium action potentials or *ultrafast* waves and compile evidence that these electrically propagated waves all move at 10–40 centimeters/sec at 20 °C.

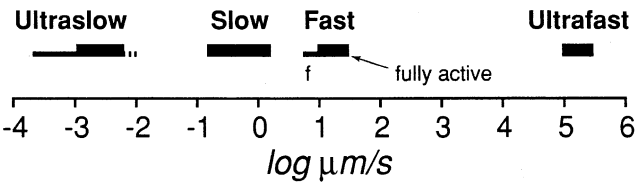

Fig. 1. A natural classification of calcium waves based upon their speeds at room temperature. Ultrafast waves refer to calcium action potentials. Fast waves through active cells refers to all such waves except for the slightly slower ones that activate eggs during fertilization that are marked (f). Fast waves are reaction-diffusion ones. Slow waves are developmental ones that are stretch propagated; while ultraslow ones are likewise develomental ones that may also be reaction-diffusion waves. (Modified from Jaffe, 1999)

* Corresponding author. Tel : 508/289-7251; Fax: 508/540-6902.
E-mail address: ljaffe@mbl.edu (L.F. Jaffe).

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2. Evidence for speed invariance

2.1. Overall

Table 1 lists the conduction speeds of those known or putative ultrafast calcium waves or calcium action potentials that I both know of and that seem to be limited by intracellular mechanisms rather than cell-to-cell delays. A third of these speeds are from cnidarian systems (as classified in Pearse et al., 1987) and these are plotted against temperature in Fig. 2; a quarter are from cardiac ones and these are plotted in Fig. 3; while envelopes around these plots together with the (extremely diverse) residual data are plotted in Fig. 4. One sees that the range of known or probable calcium action potential speeds is only about 2–4 fold at a given temperature.

Case 1 cites still useful data of Romanes on the jellyfish, *Aurelia* in 1877, well before the invention of the cathode ray oscilloscope in 1897; while case 2 cites Mayer's use of the entrapped wave method on the jellyfish, *Cassiopea* in 1914 to attain what may still be the most accurate or at least precise, single mesurement of such a speed. Technical advances such as the introduction of voltage-sensitive, fluorescent dyes have surely eased such measurements. Nevertheless, this paper is mainly made possible by the asking of a new question rather than the introduction of new methods. It is the first, extensive, comparative study of the speeds of calcium action potentials, although a 1999 paper on action potentials in a sponge does contain a valuable review of such data in plants and some invertebrates (Leys et al., 1999).

In 30 of these 127 cases, there is substantial evidence that the listed action potential is indeed propagated by calcium influx rather than sodium influx or chloride efflux. Among the cases with the most convincing evidence of relay by calcium ion influx is #30, the seminal 1985 report of Mackie and Meech on the control of slow swimming in the jellyfish, *Aglantha* by low amplitude action potentials along its giant motor axons. This report is made so convincing by the remarkable fact that the very same axons also control fast, escape-driven swimming via faster, higher amplitude sodium action potentials. A comparably convincing case of a calcium action potential is #105, the well known 1953 report of Fatt and Katz on the stimulation of the contraction of a crab's giant extensor muscles by high amplitude action potentials along them. Yet another case, 102b, would be better as a 1998 report by Kucera et al. on action potential velocities along synthetic strands reconstituted from neonatal rat heart cells. Three other, diverse and interesting – yet hitherto unrecognized or poorly known – cases of calcium action potentials are #4, #68 & #70 on such impulses along the muscle cells of various moth's hearts during systole, #128 on such impulses along the mesophyll cells of *Alrdrovanda* , a close relative of the Venus fly trap by Iijima and Sibaoka (1982) and #121–4 on such impulses along the skins of urochordates or tunicata (Bone and Mackie, 1975; Mackie and Bone, 1976–7; Anderson, 1979).

In the other 99 cases, the calcium basis of the action potential is partly inferred from the conduction velocity itself. One may consider such data selection to be 'circular reasoning' or one may consider it to result from the kind of sharp change in viewpoint that is some times called a paradigm shift. I would submit that the number and diversity of the assembled cases substantially supports the latter characterization. It is true that there are many, reliable yet unlisted cases of systems which propagate calcium action potentials yet do so at velocities which are far below the conserved range. A good example of such a low speed is the one in a sponge which is only 0.3 cm/sec at 10 °C (Leys et al., 1999) and thus about 30 times lower than the median, conserved value at that temperature. However, there is nothing in this and other such data to preclude speed reduction by cell to cell delays as well as tortuousity.

Moreover, in thirteen diverse cases (case #'s 54–62, 65, 105–6 and 125), the speed was both within the conserved range and measured along a single cell which rules out cell-cell delays. This is true of the speeds listed for the long vagal and sciatic nerves of cases #54–5 (Heinbecker and Bishop, 1931) of the speeds listed for giant brain neurons in cases #56–57 (Knowles et al., 1987) of those for (giant) Mytilus smooth, catch muscle cells in cases #61–2 (Fletcher, 1937a; Schmandt and Sleator, 1955) and in case #65 Hernandez-Nicaise et al., 1990) and of the inward wave within a striated muscle cell in case #106 (Gonzáles-Serratos, 1971) and of the wave around a single dinoflagellate cell in case #125 (Eckert, 1965).

For such reasons, our model predicts that it is the upper limit of the conduction velocities of calcium action potentials at a given temperature which should be invariant and it is that prediction which the assembled data support.

2.2. Speed invariance in Cnidaria

In considering Fig. 2 (which plots the cnidarian data), first note the speeds (encoded as blue or green) which were measured long ago on cnidarian systems with the aid of entrapped or endlessly circulating action potentials. Such endless waves can be easily started in an isolated ring of tissue which includes the edge of a jellyfish's umbrella. Started with a circumferentially polarized stimulus at one point or by a radially polarized one (likewise at one point) followed by briefly blocking the propagation of one of the resultant clockwise and counterclockwise waves (cases #2–4 via Mayer, 1914 and 1917; Kinosita, 1937). Or even started by such treatment of an intact medusa (case #5 via Mackie, 1975). Moreover, endless can mean a nondecremental wave which lasts up to eleven days and for over a million revolutions! (Mayer, 1916) One can reasonably argue that such endlesss waves offer the most reliable values for the speeds of an inherent and conserved calcium action potential mechanism.

Table 1
Speeds of action potentials that are largely limited by intracellular mechanisms and may be calcium ones. 'Yes' under 'calcium?' means that there is direct evidence that it is a calcium one. Where this evidence comes from a paper other than the main reference, it is given after 'yes'. Where this column is blank, no direct evidence is available and the probability of the action potential being a calcium one is inferred from the speed itself.

# System	cm/s at °C	calcium?	Reference
Neurons and nerve nets			
cnidaria			
1 *Aurelia* tentacular net	25 at 25		Romanes (1877)
2 *Cassiopea* isolated ring	44 at 29		Mayer (1914)
3 *Cassiopea* isolated ring	31.4 to 51.8 at 23 to 33		Mayer (1917)
4 *Mastigias* isolated ring	27 to 50 at 15 to 30		Kinosita (1937)
5 *Stomatoca* whole animal	30 at 15		Mackie (1975)
6 *Renilla* over rachis	9 at 16		Nicol (1955)
7 *Renilla*, rachis, low threshold	8 at 16		Anderson and Case (1975)
		yes	Ball and Case (1973)
8 *Geryonia*, jellyfish giant net	40 at 22		Horridge (1955)
9 *Haliclytis* subumbrella	11 at 12		Gwilliam (1960)
10 *Hydra*, longitudinal column	15 at 18		Passano and McCullough (1964)
11 *Tubularia*, polyp low threshold	16 at 19		Josephson (1965)
12 *Calliactis* slow longitudinal	5.5 at 12	yes	McFarlane (1969)
13 *Calliactis* slow around mouth	13 at 12	yes	McFarlane (1969)
14 *Obelia* hydranth	22 at 12		Morin and Cooke (1971)
15 *Corymorpha* stalk	16 at 20	yes	Ball and Case (1973)
16 *Spirocodon* 's circular swimming	18 at 19		Ohtsu and Yoshida (1973)
17 *Proboscidactyla*, tentacle	8 at 15		Spencer (1974)
18 *Hydractinia*, polyp. low threshold	18 at 18		Stokes (1974)
19 *Hydractinia* polyp lashing	9 at 18	yes	Stokes (1974)
20 *Stomatoca* preswim	43 at 15		Mackie (1975)
21 *Stomatoca* pretentacle	10 at 15		Mackie (1975)
22 *Stomatoca*, down tentacle	15 at 15		Mackie (1975)
23 *Stomatoca* around margin	13 at 15		Mackie (1975)
24 *Acanthoptilum*	13 at 19		Satterlie et al. (1976)
25 *Ptilosarcus*, a sea pen	21 at 18		Satterlie et al. (1976)
26 *Millepora*, the fire coral	25 at 26		Kruif (1976 a, b)
27 *Polyorchis* preswim	18 at 14		Spencer (1978)
28 *Polyorchis* pretentacle	47 at 14	yes	Spencer (1978)
29 *Polyorchis*	18 at 14		Spencer (1978)
30 *Aglantha* low-threshold	25 at 12	yes	(Mackie and Meech, 1985)
ctenophores			
31 *Mnemiopsis*, along canal	14 at 24		Chang (1954)
32 *Pleurobrachia* ciliary waves	8 at 17		Sleigh (1968)
bryozoa			
33 *Flustrellidra*, through colony	25 at 22		Thorpe (1982)
mollusca			
34 *Aplysia* parapodial nerve	40 at 21		Fröhlich (1910)
35 *Ariolimax* (slug) pedal nerve	37 at 22		Carlson (1911)
38 *Ariolimax* pedal nerve	60 at 20		Turner and Nevius (1951)
39 *Mya*'s connective	25 at 17		Horridge (1958)
40 *Loligo* gut	12 at 21		Prosser et al. (1965)
crustaceans			
41 *Homarus* intestine	≤ 20 at 21		Prosser et al. (1965)
42 *Callinectes* intestine	25 at 21		Prosser et al. (1965)
worms			
43 *Phascolosoma* 's proboscis	30 at 24		Prosser and Melton (1954)
44 a flatworm's nerve cord	34 at 22		Keenan et al. (1984)
45 *Ascaris* dorsal motoneurons	28 at 38		Walrond and Stretton (1985)
		yes	(Weisblat and Russell, 1976)
echinoderms			
46 *Thyone* retractor	26 at 24		Prosser et al. (1951)
47 *Cucumaria* radial nerve	17 at 26		Pople and Ewer (1954)

# System	cm/s at °C	calcium?	Reference
48 *Cucumaria* circumoral nerve	11 at 22		Pople and Ewer (1955)
49 *Strongylocentrotus* radial nerve	17 at 22		Sandemann (1965)
50 *Ophiosila* 's radial nerve	35 at 15	yes	Brehm (1977)
51 *Diadema* spines' neurites	27 at 22	yes	Berrios et al. (1985); Smith et al. (1985)
tunicates			
52 *Corella* branchial nerve net	20 at 22	yes	Mackie et al. (1974)
vertebrates			
53 turtle 's penis retractor	15, 27, 41 at 5, 13, 21		Hoffman (1913)
54 turtle vagus	38 at 23		Heinbecker and Bishop (1931)
55 frog sciatic/autonomic	50 at 23		Heinbecker and Bishop (1931)
56 cavy hippocampal mossy axon	40 at 36		Knowles et al. (1987)
57 cavy hippocampal Schaffer axons	50 at 36		Knowles et al. (1987)
58 monkey visual cortex	_25 at 37		Grinvald et al. (1994)
59 rat neocortical dendrite	15, 40 at 22, 35	yes	Stuart and Sakmann (1994)
60 rat neocortical axon	30 at 35		Stuart et al. (1997)
60a turtle visual cortex	~70 at 23		Prechtl et al. (1997)
60b turtle visual cortex	18 at 21		Colombe and Ulinski (1999)
60c turtle visual cortex	~30 at 23		Prechtl et al. (2000)
60d ferret visual cortex	~30 at 37		Roland (2002)
Protozoan Muscle			
60d *Carchesium* stalk muscle	≤ 60 at 22		Sugi (1960)
Smooth Muscles			
61 *Mytilus* catch muscle	18 at 16		Fletcher (1937a)
		yes	(Twarog, 1967; Fletcher, 1937b)
62 *Mytilus* catch muscle	22 at 23	yes	Schmandt and Sleator (1955)
64 *Cestum* (ctenophore) body	15 at 22		Pfitzner (1962)
65 *Beröe* giant longitudinal cells	45 at 21	mainly	Hernandez-Nicaise et al. (1990)
66 cavy's taenia coli	14 at 37	yes	Stevens et al. (1999)
Cardiac Muscles			
4 *Telea* moth	12 at 21		Tenney (1953)
		yes	(McCann, 1971; Carrington and Tenney, 1959)
68 *Samia* moth	22 at 24		McCann (1964)
		yes	(McCann, 1971)
70 *Manduca* moth	9.6 at 20	yes	Smits et al. (2000)
3 *Ciona*, a tunicate	9, 20 at 10, 20		Weiss et al. (1976); Morad and Cleeman (1980)
		yes	(Kriebel, 1967, 1969)
72 *Rana* ventricle strips	10 at 18		Bammer (1953)
2 *Rana* ventricle strips	4–17 at 3–30		Heintzen (1954)
73 frog isolated ventricle	25 at 24		Irisawa et al. (1965)
74 *Rana* isolated hearts ventricle	10 at 20		Dillon and Morad (1981)
75 *Rana* atrium piece	25 at 24		Sawanobori et al. (1981)
77 *Rana* whole atrium	22 at 27		Komuro et al. (1986)
78 whole *Pseudomys* turtle ventricle	16 at 19		Burggren (1978)
79 whole *Testudo* tortoise ventricle	13 at 19		Burggren (1978)
80 fused chick embryo heart parts	<67 at 39	yes	(Sakai et al., 1983) Olivo (1948)
79a 3-day chick embryo atrium	53* at 38	yes	(Sakai et al., 1983) Yoshigi et al. (1997)
81 14-day chick embryo atrium	40 at 33		Lieberman and Paes de Carvalho (1965)
5 7-day chick embryo ventricle	20 at 30		DeJong et al. (1992)
		yes	(Sakai et al., 1983)
82 various ventricles	30 at 38		Scherman et al. (1953)
84 calf longitudinally	48 at 25		Clerc (1976)
85 cow ventricle longitudinal	50 at 25		Weingart (1977)
86 isolated pig heart's ventricle	50 at 39		Kléber et al. (1986)
87 open chested pig's ventricle	53 at 39		Harper et al. (1993)
88 rabbit ventricle	50 at 25		Cranefield (1975)
88a sheep ventricle	33 at 37		Pertsov et al. (1993); Beaumont et al. (1998)
89 rabbit ventricle	40 at 36		Sung et al. (2000)

# System	cm/s at °C	calcium?	Reference
91 open chested dog's ventricle	68 at 38.5		Taccardi et al. (1994); Muzikant and Henriquez (1998)
92 rabbit ventricle prep	52 at 36.8		Knisley and Hill (1995)
93 rabbit papillary muscle	48 at 37		Fleischauer et al. (1995)
95 cavy papillary prep	37 at 36		Hisatome and Arita (1995)
96 isolated cavy heart's ventricle	73 at 36		Girouard et al. (1996); Winfree (1998)
97 isolated adult mouse ventricle	32 at 31		Guerrero et al. (1997)
98 isolated neonatal mouse vent.	20 at 31		Guerrero et al. (1997)
99 open chested left mouse vent.	35 at 37		Verheule et al. (1999)
100 open chested right mouse vent.	50 at 37		Verheule et al. (1999)
101 isolated mouse atrium	38 at 31		Thomas et al. (1998)
102 open chested mouse atrium	55 at 37		Verheule et al. (1999)
102a reconstituted chick strands	34 at 37 [not plotted]		Lieberman (1973)
7 reconstituted rat strands	45 at 36		Kucera et al. (1998)
103 reconstituted rat strands	27 at 35		Fast and Ideker (2000)
104 isolated human heart's ventricle	36 at 37		Durrer et al. (1970)
6 open chested human atrium	80 at 37		Hannson et al. (1998)
Striated Muscles			
105 *Portunas* crab extensor	29 at 21		Fatt and Katz (1953)
		yes	Fatt and Ginsborg (1958)
106 frog semitendinosus (inward wave)	2.7 –8.9 at 5–21	yes	Gonzáles-Serratos (1971)
Epithelia			
Cnidaria (Coelenterates)			
106a *Sarsia*, ectoderm	15 at 18		Mackie and Passano (1968)
107 *Sarsia* endoderm	23 at 18		Mackie and Passano (1968)
108 *Euphysa* endoderm	35 at 20		Mackie and Passano (1968)
109 *Phialidium*, ectoderm	19 at 20		Mackie and Passano (1968)
110 *Euphysa*, ectoderm	20 at 20		Mackie and Passano (1968)
111 *Euphysa* ectoderm	10 at 11	yes	Josephson and Schwab (1979)
112 *Nanomia* bract ectoderm	34 at 20		Mackie and Passano (1968)
113 *Nanomia* stem endoderm slow	20 at 13		Spencer (1971)
114 *Nanomia* stem endoderm slow	30 at 14		Mackie (1978)
115 *Proboscidactyla* stolon	7.3 at 13		Spencer (1974)
116 *Stomatoca* endoderm	11 at 15		Mackie (1975)
117 *Hippopodius* endoderm	10 at 21	yes	Mackie (1976)
118 *Polyorchis* ectoderm	9 at 14		Spencer (1978)
119 *Polyorchis* endoderm	8 at 14		Spencer (1978)
120 *Forskalia* stem	40 at 20		Mackie (1978)
Urochordate or Tunicata			
121 *Oikopleura* (Larvacea) skin	18 at 12		Bone and Mackie (1975)
122 an ascidian tadpole's skin	7 at 20		Mackie and Bone (1976)
123 *Salpa* (Thaliacea) skin	17 at 18		Mackie and Bone (1977)
124 *Salpa* stolon skin	6 at 21	yes	Anderson (1979)
Photosynthetic Organisms			
125 *Noctiluca*, a dinoflagellate	16 at 22		Eckert (1965)
126 *Nitella* in pond water**	~30 at rm	yes	(Kikuyama and Tazawa, 1998) Sibaoka (1958)
127 Venus fly-trap (rosales) along bundles	15 at 22		Sibaoka (1966)
128 *Aldrovanda* (rosales)	10 at 22	yes	(Iijima and Sibaoka, 1985) Iijima and Sibaoka (1982)

*wave front velocity

** about ten times faster than the speeds seen in the moist air which is some times used.

Direct evidence that they are calcium action potentials lies in several facts. First, a small extension of the curve representing case #4 (for *Mastigias* , a close Pacific relative of the better known *Cassiopea*) reaches the point representing case #30 for *Aglantha* which was measured at the relatively slow speed of its unarguably calcium-based action potential by Mackie and Meech,1985. Moreover, a close reading of Kinosita's (understandably) forgotton 1937 paper– the one which reports the work on entrapped waves in *Mastigias* – shows evidence that these waves are low amplitude ones.

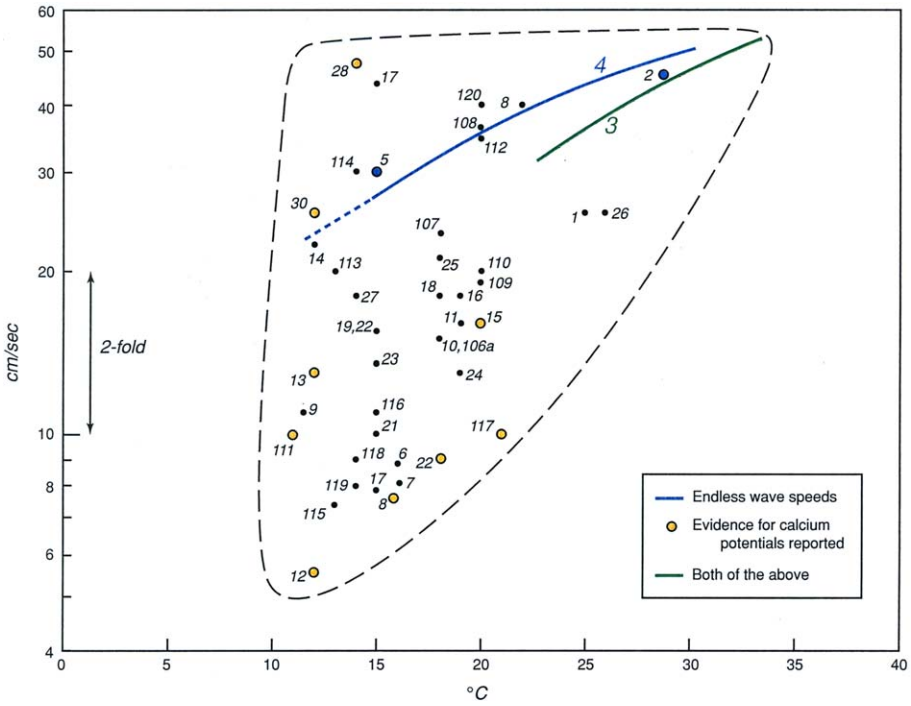

Fig. 2. Cnidarian action potential speeds versus temperature for the case #'s in Table 1.

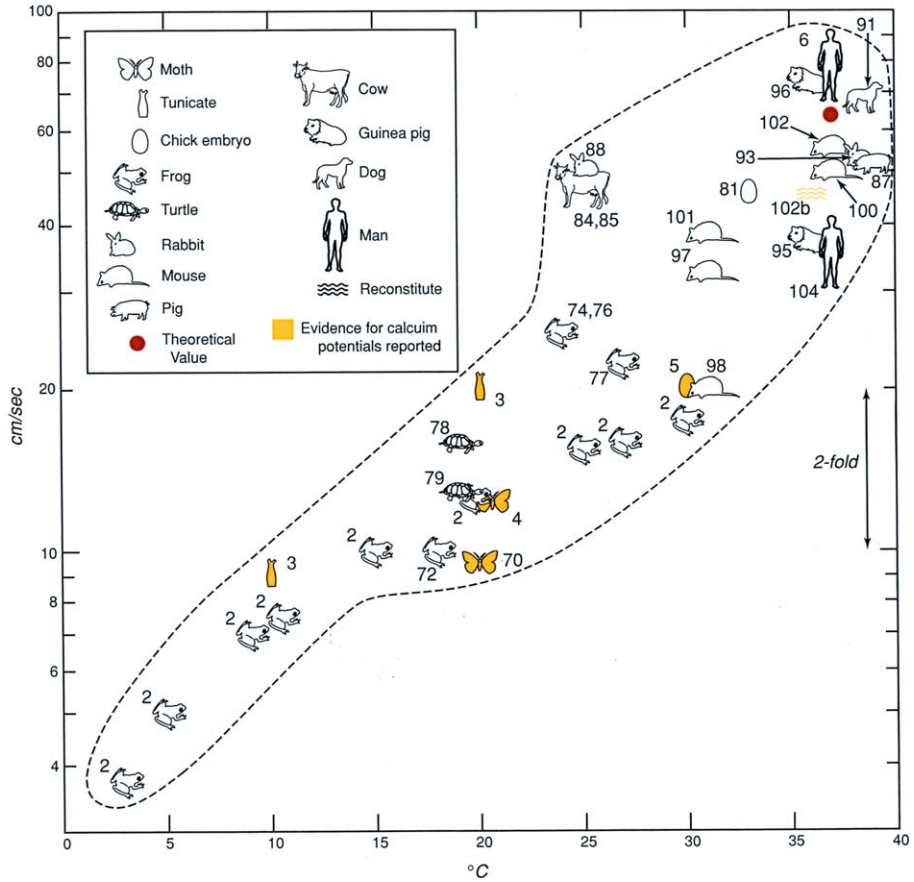

Fig. 3. Cardiac action potential speeds versus temperature for the case #'s in Table 1. The red circle at 62 cm/sec and 37 °C is a recent theoretical value for velocity through working muscles of the human heart (Hinch, 2002).

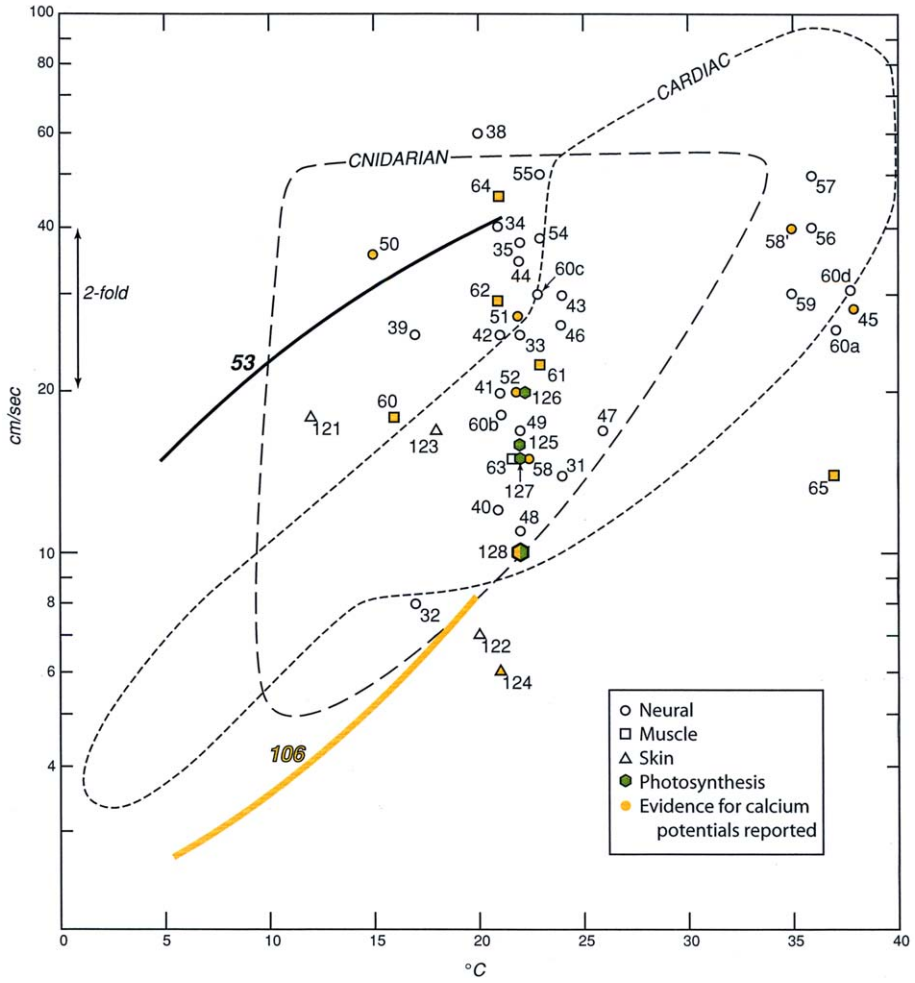

Fig. 4. Action potential speeds versus temperature for all of the case #'s in Table 1. The cnidarian and cardiac data are represented by envelopes from Fig. 2 and 3 respectively. Other speeds are shown via case numbers and coded symbols.

Second, the similar curve for case #3 – with values for *Cassiopea* itself – comes from Mayer's 1917 paper which includes a report of magnsium suppression of such action potentials.

Altogether, the reports behind the 45 cnidarian action potential speed points or lines that are listed in Table 1 provide direct evidence that nine of them are calcium-based. One of these, of course, is the conclusive one of *Aglantha* The other eight include case #111 for which action potential continuation in sodium free media is reported and the rest which all report Mg^{++} suppression and/or report tetrodotoxin independence. Moreover, four of the cases for which there is evidence for calcium-based action potentials are for ones believed to be carried by epithelia rather than neurons or nerve nets.

2.3. Speed invariance in working cardiac muscles

Fig. 3 displays the speeds of action potentials down working heart muscles in 40 cases from moths to men. Restriction to a two to three-fold speed range at a given temperature is apparent. One must emphasize that these data are restricted to working muscles. The higher speeds through the specialized, high speed conduction systems of the adult vertebrate heart are not included. Thus the high speeds of action potentials through Purkinje tissue are omitted. Also left out are speeds through tissues specialized to delay impulse conduction. Thus the low speeds of action potentials through the junctional fibers connecting the atrium and the ventricle are omitted (Burggren, 1978) These data extend from 3 to 40 °C with a collective rise per 10 °C or Q_{10} of about two-fold. A key to knowledge of such a wide temperature range is case #2 taken from the excellent but apparently forgotton paper of Heintzen (1954). This paper reports conduction speeds down frog ventricular strips measured at temperatures from 3 to 30 °C. Moreover, the displayed speeds lie in a restricted range over a remarkable range of system integrity. Thus they do so in measurements made on open chested mammals from mice to men, on various isolated heart parts and even on synthetic strands of tissue that are reconstituted from cultured embryonic chick cardiomyocytes (case # 102a from Lieberman, 1973, and from rat cardiomyocytes (cases #17 and # 103 from Kucera et al., 1998 and from Fast and Ideker, 2000 respectively). Altogether, the narrow speed ranges shown in Fig. 3 suggest that similar ionic mechanisms drive

all of these action potentials. So one must ask if they are all sodium action potentials or are they all calcium ones.

The present consensus view of the ionic basis of human heart action potentials is clearly expressed in a recent theoretical review and analysis by Hinch (2002). It deduces the velocity of 62 cm/sec at 37 °C shown in red in Fig. 3 on the assumption that cardiac action potentials are propagated by sodium entry. It sees a rise in intracellular calcium as a primary stimulus of heart cell contraction. Moreover, it refers to several recent theoretical papers for more detailed consideration of calcium handling. Thus it refers to Luo and Rudy (1994) who consider the roles of calcium increases during relatively late phases of the cardiac actional potential rather than in the basic, Hodgkin-Huxley type propagation mechanism. A more clinical presentation of the consensus view appears in a 1998 textbook on "Basic Cardiac Electrophysiology for Clinicians" (Jalife et al., 1999) on p. 107 of which it is written that, ″In the working atrial and ventricular muscle cells… Na currents provide the largest fraction of the excitatory current. In the [pacemaker]..nodes, on the other hand, inward current during the action potential upstroke is largely provided by the Ca channels″. Moreover, an even more sodium-centered view of action potential conduction in the healthy human heart is presented by Fozzard in a 1979 volume of the authoritative Handbook of Physiology. Nevertheless, the data which we have assembled suggest that the action potentials which travel down the working muscles of all healthy hearts are calcium ones.

Evidence for calcium rather than sodium action potentials is available for the three moth hearts studied (cases #4, #68 and #70 from Tenney (1953), McCann (1964) and Smits (2000) and for the tunicate one (case #3 from Weiss et al., 1976; Morad and Cleeman, 1980) and for the reconstituted rat heart strands (case # 7 and #102). In the moths, the evidence lies in the very low ratio of sodium to calcium ions found in the haemolymph of these plant eaters. Moth haemolymph [Ca^{2+}] has the unsurprising value of 10 mM but it's sodium can be so low as to be "barely detectible" (Carrington and Tenney, 1959). This because these moths feed only on plants which in turn live in low sodium soils and consequently contain very little sodium. Moreover, in an open heart preparation of another plant eating insect, cecropia, no action potentials are seen in nominally calcium-free media; the voltage peak rises 22 mV/decade of added calcium; while added sodium or tetrodotoxin have no effect. Surely, these moths' action potentials are sodium ones. In tunicates, the matter has been little studied but the available evidence does favor calcium rather than sodium action potentials: In isolated, single-cell-thick hearts of the sea potato, *Boltenia*, tension changes in response to luminal [Ca^{2+}] and [Mg2+] changes as would be expected for calcium action potentials while 50% reductions of [Na^{+}] have no effect (Kriebel, 1969). In strands reconstituted from neonatual rats, action potentials are demonstrably propagated by calcium entry when [K^{+}] levels are raised from the normal blood level of 5.8 mM up to 14.8 mM (Kucera et al., 1998). So one is led to ask what the levels of [K^{+}] are within the thin extracellular or 'interstitial' spaces of healthy mammalian hearts. An attempt to measure such [K^{+}] levels within healthy pig hearts – one done with ion specific electrodes – suggests that it is actually about 30 mM and thus far above the normal blood level (Hill and Gettes, 1980). This since this high value was the one measured right after electrode insertion. Perhaps the subsequent, slow fall *precisely* to blood levels resulted from leakage around the 1.5 mm wide. electrodes used. Moreover, earlier studies of interstitial potassium levels in frog ventricular strips also showed extracellular potassium to be far above the 3 mM bath level right after impalement or insertion of a (gross) potassium electrode into the extracellular space. A difference that likewise lasted for a few minutes (Kline and Morad, 1976 and 1978; reviewed by Cohen and Kline, 1982). Moreover, the inferred high levels of interstitial potassium have an interesting precedent in the high (160 mM) potassium levels known to exist within the cochlear endolymph (Brown, 1999).

2.4. Speed invariance in other systems

Fig. 4 shows envelopes of the cnidarian and cardiac data together with the data from the other fifty or so cases listed in Table 1. Two thirds of the latter concern action potentials in neural systems and evidence is available in a third of these that they are calcium rather than sodium action potentials. The evidence for calcium action potentials along the spines of a sea urchin, *Diadema* is strongest. For they continue in Na-free media but are abolished in Ca-free ones; are unaffected by tetrodotoxin but are blocked by 2–5 mM La^{3+}, Co $^{2+}$, Cd $^{2+}$ and by 2 mM concentrations of the organic calcium channel blocker, Bepridil (case #51 via Smith et al., 1985). The evidence for calcium action potentials in other such cases is not that strong but is still substantial. Thus the action potentials along the radial nerve chord of a starfish are unaffected by sodium removal and are blocked by calcium removal (case#50, via Brehm, 1977). While the regenerative potentials in the distal apical dendrites of young rat pyramidal dendrites are blocked by 0.2 mM Cd^{++} in the medium and are accompanied by large intracellular calcium increases (case # 59 via Stuart and Sakmann, 1994). The next largest group of 'other' systems involve action potentials down smooth muscles. Here the evidence for calcium based action potentials is so strong, so long standing and so general that Aidley's authoritative, recent textbook on "The Physiology of Excitable Cells" writes that "the principal inward current during the action potential [in smooth muscles generally] must be via calcium channels rather than sodium channels." (Aidley, 1998). Moreover, Table 1 lists sources of evidence of such calcium dependence in those particular cases where this is available. Finally, there is a group of about 8 cases which include action potentials along urochordate skin (cases #121–124 via Bone and Mackie, 1975; Mackie and Bone, 1976–7; Anderson, 1979), inward or centripetal action potentials in a striated vertebrate muscle (case #106 via

Gonzales-Serratos, 1971) and action potentials within a dinoflagellate (case # 125 via Eckert, 1965) and within insectivorous plants (cases # 126–128 via Burdon-Sanderson, 1882; Sibaoka, 1966; Iijima and Soibaoka, 1982). The inward action potential speed in striated muscle of case#106 is surely one along T tubules and these are thought to be sodium ones. However, this belief relies on old observations that such action potentials contiinue in calcium-free media even though turnover of cytosolic calcium through T tubules is far too fast for such observations to rule out inward calcium action potentials in striated muscle cells. Insectivorous plants live in soils with far too little sodium for sodium action potentials to be possible so the only issue is whether the observed ones are calcium or chloride based. The 1985 paper of Iijima and Sibaoka indicates that they are, in fact, calcium ones.

Thus the action potential's amplitude rises 26 mV per tenfold rise in extracellular Ca^{2+}, is blocked by 2.5 mM La^{+3} etc.

3. Explaining the invariance of calcium action potential speeds

The 2–4 fold range of natural calcium action potential speeds contrasts with the thousand-fold one found for natural sodium action potential speeds. This thousand-fold figure was obtained from top speeds of 27 meters/sec and 45 m/sec for sodium action potentials traveling down squid giant axons (Hodgkin, 1939) and down the median giant fiber of the common earthworm (Bullock, 1945) respectively together with a minimal speed of 0.045 m/sec for sodium action potentials traveling along the skin of young tadpoles of the common toad (Roberts and Stirling, 1971). Since the latter was believed to be propagated via direct current flow through gap junctions, the molecular mechanisms over this thousand-fold range should be comparable. This does not seem surprising but serves to emphasize that the far narrower range of calcium action potential speeds calls for an explanation.

The factors which limit conduction velocities in epithelia are not fully established in the sense that no theory of action potentials along sheets as opposed to cylinders has been published. However, it is easy to show that the volume to surface ratio of a sheet is four times that of a cylinder. Since established theory (Hunter et al., 1975) shows conduction velocity to vary with the square root of this ratio, epithelial speeds would be expected to be twice that of cylindrical ones. Yet an analysis (not shown) of the epithelial v.s. the cylindrical data in Fig. 2 actually shows some tendency for the epithelial speeds to be lower. This subsidiary analysis is consistent with the idea that the conserved conduction velocity values of calcium action potentials are set by near surface or cortical mechanisms rather than the extended currents of established action potential theory.

One also sees that the speeds that are assembled from diverse systems in Fig. 2 rise exponentially with temperature and do so with a Q_{10} which is visibly comparable to the Q_{10} 's of several particular systems shown on the same graph. Moreover, a regression analysis of the plotted points yields an assembly value of 1.62 ± 0.23 fold per 10 °C which is not significantly different from the value of 1.70 ± 0.03 measured for squid axon action potentials (Chapman, 1967). Of course, the squid axon's action potential is the classical sodium one while it is my hypothesis that the values assembled here are ones for calcium action potentials. However, I know of no reason to believe that the temperature dependence of sodium and of calcium action potential conduction velocities will prove to differ very much. So in the absence of any well studied model system for calcium action potentials which is comparable to the squid axon one for sodium action potentials, the similarity of the assembly' Q_{10}'s and of the squid axon's Q_{10} can be taken as substantial, further support for a highly conserved calcium action potential mechanism.

Classical extended current theory predicts that conduction velocities along cylindrical systems will rise with the square root of their widths. In order to test this prediction, I have made a list of the widths of the various cylindrical cells which propagated the action potentials listed in Table 1. Despite a known 300-fold width range and thus an expected speed range of about 17-fold, no correlation between calcium action potential speed and cell width could be seen. Thus the speeds along cells that are about 30 microns thick (cases # 30 and 65 for giant *Aglantha* axons and *Beröe* longitudinal smooth muscles respectively) are not noticeably different from those along cells that are 0.1 to 0.2 microns thick (cases # 24, 10 and 54 for *Acanthoptilum, Hydra* and turtle vagus nerve nets or neurons respectively). This width independence provides good evidence for a cortical as opposed to an extended current explanation for calcium action potential invariance.

A subsurface or cortical, yet conservative one is that evolution has driven calcium action potentials to the highest speeds that avoid calcium poisoning by excessive entry rates into the cell cortex. Pressures for yet higher speeds led to the invention of sodium action potentials whose speeds are surely not limited by sodium poisoning.

An alternative explanation – suggested by consideration of the conservation of both fast and slow calcium wave speeds (Jaffe and Créton, 1998) – is that ultrafast calcium action potentials are propagated by an ancient, multiprotein machine so complex that once it was invented its speed could not be changed by evolution. What Kemphues has recently called a core cassette of interacting proteins. If this were true, than calcium action potentials or ultrafast calcium waves would be propagated by another conserved wave machine. Nevertheless, this concept does *not* seem applicable to the conservation of ultrafast calcium wave speeds. For in those larger cells which propagate such waves (such as *Aglantha)* calcium influx at the waves' peak would yield propagation speeds far higher than the conserved and observed values. And what would have prevented the evolution of cells with such higher influxes via a rise in the abundance and/or conductance of their voltage-sensitive channels? Indeed, *in* the

prototypical giant axons of *Aglantha*, just such an evolution would seem to underlie the presence of both relatively slow calcium action potentials and relatively fast sodium ones. However, the plasma membrane machine which drives ultrafast calcium waves seems to involve far fewer kinds of key proteins than the ones in endoplasmic reticulum which drive fast and slow calcium waves. So the complexity which justifies conservation *by* complexity in fast and slow waves does not seem to exist in ultrafast ones. So one seems compelled to support an evolutionary mechanism centered on speed limitation by calcium poisoning for ultrafast calcium waves.

Looking forward, one may ask which systems might best allow the molecular pursuit of calcium action potentials. What might be the squid axon of such waves? One attractive possibility are *Physarum* plasmodia since these acellular slime molds grow to as much as 30 cm in diameter on forest floors where integrating action potentials should be advantageous yet sodium and chloride ions are very sparse. It is easy to grow huge amounts of *P. polycephalum* for biochemical analysis; moreover, they are aerial organisms in which action potential speeds could be easily recorded with crude extracellular electrodes, voltage sensitive dyes or even with injected, chemiluminescent, calcium-reporting aequorins (Sauer, 1982). Large and natural (although slow) oscillations of calcium ion concentration have been measured in *Physarum* with the aid of injected aequorin (Ridgway and Durham, 1976); moreover, there is even an old report which suggests the presence of action potentials in *Physarum* (Tasaki and Kamiya, 1950). Why not look directly for calcium action potentials in *Physarum* with injected aequorin?

Finally, I would urge the theoreticians to consider calcium action potentials. Their work continues to be central to our understanding of sodium action potentials. Why not extend it to calcium ones?

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References

Aidley, D.J., 1998. The Physiology of Excitable Cells. 4th ed. Cambridge University Press, Cambridge.

Anderson, P.A.V., Case, J.F., 1975. Electrical activity associated with luminescence and other colonial behavior in the pennatulid *Renilla kollikeri*. Biol. Bull. 149, 80–95.

Anderson, P.A.V., 1979. Epithelial conduction in salps I. Properties of the outer skin pulse system of the stolon. J. exp. Biol. 80, 231–239.

Ball, E.E., Case, J.F., 1973. Electrical activity and behavior in the solitary hydroid *Corymorpha Palma* II. Conducting systems. Biol. Bull. 145, 243–264.

Bammer, H., 1953. Die Beziehungen zwischen der Reizfrequenz und der Geschwindigkeit der Erregungsleitung im Herzmuskel. Zges. exptl. Med. 121, 488–496.

Beaumont, J., Davidenko, N., Davidenko, J.M., Jalife, J., 1998. Spiral waves in two-dimensional models of ventricular muscle: Formation of a stationary core. Biophys. J. 75, 1–14.

Berrios, A., Brink, D., del Castillo, J., Smith, D.S., 1985. Some properties of trhe action potentials conducted in the spins of the sea urchin *Diadema antillarum*. Comp. Biochem. Physiol. 81A, 15–23.

Bone, Q., Mackie, G.O., 1975. Skin impulses and locomotion in *Oikopleura* (tunicata: larvaceae). Biol Bull. 149, 267–286.

Brehm, P., 1977. Electrophysiology and luminescence of an ophiuroid radial nerve. J. exp. Biol. 71, 213–227.

Brown, M.C., 1999. Audition. In: Zigmond, M.J. (Ed.), Fundamental Neuroscience. Academic Press, San Diego, pp. 795.

Bullock, T.H., 1945. Comparative aspects of superficial conduction systems in echinoids and asteroids. J Neurophysiol 8, 55–71.

Burdon-Sanderson, J., 1882. On the electromotive properties of the leaf of *Dionea* in the excited and unexcited states. Phil. Trans. Roy. Soc. London 173, 1–55.

Burggren, W.W., 1978. Influence of intermittent breathing on ventricular depolarization patterns in chelonian reptiles. J. Physiol. (London) 278, 349–364.

Carlson, A.J., 1911. The effects of stretching the nerve on the rate of conduction of the nervous impulse. Am. J. Physiol. 27, 323–330.

Carrington, C.G., Tenney, S.M., 1959. Chemical constituents of haemolymph and tissue in *Telea polyphemus* Cram. J Ins Physiol. 3, 402–413.

Chang, J.J., 1954. Analysis of the luminescent response of the ctenophore, *Mnemiopsis Leidyi*, to stimulation. J Cell Comp Physiol. 44, 365–394.

Chapman, P.A., 1967. Dependence on temperature of the conduction velocity of the action potential of the squid giant axon. Nature 213, 1143–1144.

Clerc, L., 1976. Directional differences of impulse spread in trabecular muscle from mammalian heart. J Physiol 255, 335–346 (London).

Cohen, I., Kline, R., 1982. K^+ fluctuation in the extracellular spaces of cardiac muscle. Circ. Res. 50, 1–16.

Colombe, J.B., 1999. Temporal dispersion windows in cortical neurons. J. Computational Neuroscience 7, 71–87.

Cranefield, P.F., 1975. The Conduction of the Cardiac Impulse Futura. Mount Kisco, New York.

DeJong, F., Opthof, T., Wilde, A.A.M., Janse, M.J., Charles, R., Lamers, W.H., Moorman, A.F.M., 1992. Persisting zones of slow impulse conduction in developing chicken hearts. Circ Res 71, 240–250.

Dillon, S., Morad, M., 1981. A new laser scanning system for measuring action potential propagation in the heart. Science 214, 453–456.

Durrer, D., Van Dam, R.T., Freud, G.E., Janse, M.J., Meijer, F.L., Arzbaecher, R.C., 1970. Total excitation of the isolated human heart. Circulation 41, 899–912.

Eckert, R., 1965. Bioelectric control of bioluminescence in the Dinoflagellate, *Noctiluca*. Science 147, 1140–1145.

Fast, V.G., Ideker, R.E., 2000. Simoultaneous optical mapping of transmembrane potential and intracellular calcium in myocyte cultures. J. Cardiovasc. Electrophysiol. 11, 547–556.

Fatt, P., Ginsborg, B.L., 1958. The ionic requirements for the production of action potentials in crustaceans muscle fibres. J Physiol. (London) 142, 516–543.

Fatt, P., Katz, B., 1953. The electrical properties of crustacean muscle fibres. J. Physiol. 120, 171–204 (Lond.).

Fleischauer, J., Lehmann, L., Kléber, A.G., 1995. Electrical resistances of interstitial and microvascular space as determinants of the extracellular electrical field and velocity of propagation in ventricular myocardium. Circulation 92, 587–594.

Fletcher, C.M., 1937a. Action potentials recorded from an unstriated muscle of simple structure. J Physiol. 90, 233–253 (London).

Fletcher, C.M., 1937b. Excitation of the action potential of a molluscan unstriated muscle. J Physiol. 90, 415–428.

Fröhlich, F.W., 1910. Experimentelle Studien am Nervensystem der Mollusken 10. Z. allg. Physiol. 11, 141–144.

Gilkey, J.C., Jaffe, L.F., Ridgway, E.B., Reynolds, G.T., 1978. A free calcium wave traverses the activating egg of the medaka, *Oryzias latipes*. J. Cell Biol. 76, 448–466.

Girouard, S., Pastore, J., Lauritka, K.R., Gregory, K.W., Rosenbaum, D.S., 1996. Optical mapping in a new guinea pig model of ventricular tachycardia reveals mechanisms for multiple wavlengths in a single reentrant circuit. Circulation 93, 603–613.

Gonzáles-Serratos, H., 1971. Inward spread of actvation in vertebrate muscle fibres. J. Physiol. (London) 212, 777–799.

Grinvald, A., Lieke, E.E., Frostig, R.D., Hildesheim, R., 1994. Cortical point-spread function and long-range lateral interactions revealed by real-time optical imaging of macaque monkey primary visual cortex. J. Neurosci. 14, 2545–2568.

Guerrero, P.A., Schuessler, R.B., Davis, L.M., Beyer, E.C., Johnson, C.M., Yamada, K.A., Saffitz, J.E., 1997. Slow ventricular conduction in mice heterozygous for a connexin43 mutation. J. Clin. Invest. 99, 1991–1998.

Gwilliam, G.F., 1960. Neuromuscular physiology of a sessile scyphozoan. Bio. Bull. 119, 454–473.

Hadjikhani, N., Sanchez del Rio, M., Wu, O., et al., 2001. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Nat Ac Sc (USA) 98, 4687–4692.

Hansson, A., Holm, A., Blomström, P., Johansson, C., Lührs, C., Brandt, J., Olsson, S.B., 1998. Right atrial free wall conduction velocity and degree of anisotropy in patients with stable sinus rhythm studied during open heart surgery. Eur Heart J 19, 293–300.

Harper, J., Johnson, T.A., Engle, C.L., Martin, D.G., Fleet, W., Gettes, L.S., 1993. Effect of rate on changes in conduction velocity and extracellular potassium concentration during acute ischemia in the in situ pig heart. J Cardiovasc Electrophysiol 4, 661–671.

Heinbecker, P., Bishop, G.H., 1931. Effect of anoxemia, carbon dioxide and lactic acid on electrical phenomena of myelinated and unmyelinated fibres of the autonomic nervous system. Am. J. Physiol. 96, 613–627.

Heintzen, P., 1954. Untersuchungen über die Temperaturabhängigkeit der elekrischen Errengsvorgänge am Froschherzen. Pflügers Arch. 259, 381–399.

Irisawa, H., Hama, K., Irisawa, A., 1965. Mechanisms of slow conduction at the bulbo-ventricular junction. Circ Res 17, 1–10.

Hernandez-Nicaise, M.L., Mackie, G.O., Meech, R.W., 1980. Giant smooth muscle cells of *Beröe*. J. Gen. Physiol. 75, 79–105.

Hill, J.L., Gettes, L.S., 1980. Effect of acute coronary artery occlusion on local myocardial extracellular K^+ activity in swine. Circulation 61, 768–778.

Hinch, R., 2002. An analytical study of the physiology and pathology of the propagation of cardiac action potentials. Prog Biophys Molec Biol 78, 45–81.

Hisatome, I., Arita, M., 1995. Effects of catecholamines on the residual sodium channel dependent slow conduction in guinea pig ventricular muscles under normoxia and hypoxia. Cardiovasc Res 29, 65–73.

Hodgkin, A.L., 1939. The relation between conduction velocity and the electrical resistance outside a nerve fibre. J. Physiol. (London) 94, 560–570.

Hoffman, P., 1913. Einige Versuche zur allgemeinen Muskelphysiologie an einem sehr günstigen Objekte (Retractor penis der Schildkrote). Zeit Biol. 61, 311–325.

Horridge, G.A., 1955. The nerves and muscles of medusae II. *Geryonia proboscidalis* Eschscholztz. J exp Biol. 32, 555–568.

Horridge, G.A., 1958. Transmission of excitation through the ganglia of *Mya* (lamellibranchiata). J Physiol (London) 143, 553–572.

Hunter, P.J., McNaughton, P.A., Noble, D., 1975. Analytical models of propagation in excitable cells. Prog Biophys Molec Biol 30, 99–144.

Iijima, T., Sibaoka, T., 1982. Propagation of action potential over the traplobes of *Aldrovanda vesiculosa*. Plant & Cell Physiol 23, 679–688.

Iijima, T., Sibaoka, T., 1985. Membrane potentials in excitable cells of *Aldrovanda vesculosa* trap-lobes. Plant Cell Physiol. 26, 1–13.

Jaffe, L.F., 1993. Classes and mechanisms of calcium waves. Cell Calcium 14, 736–745.

Jaffe, L.F., 1999. Organization of early development by calcium patterns. BioEssays 21, 657–667.

Jaffe, L.F., Créton, R., 1998. On the conservation of calcium wave speeds. Cell Calcium 24, 1–8.

Jalife, J., Delmar, J., Davidenko, J.M., Anumonwo, J.M.B., 1999. Basic Cardiac Electrophysiology for the Clinician Futura. Armonk, NY.

Josephson, R.K., 1965. Three parallel conducting systems in the stalk of a hydroid. J Exp Biol 42, 139–152.

Josephson, R.K., Schwab, W.E., 1979. Electrical properties of an excitable epithelium. J Gen Physiol 74, 213–236.

Keenan, L., Koopowitz, H., Solon, M.H., 1984. Primitive nervous systems: Electrical activity in the nerve cords of the parasitic flatworm, *Gyrocotyle fimbriata*. J Parasit 70, 131–138.

Kikuyama, M., Tazawa, M., 1998. Temporal relationship between action potential and Ca2+ transient in characean cells. Plant Cell Physiol. 39, 1359–1366.

Kinosita, H., 1937. The "entrapped circuit wave" in a scyphomedusa, *Mastigias papua*. Zool Mag (Tokyo) 49, 437–455.

Kléber, A.G., Janse, M.J., Wilms-Schopmann, F.J.G., Wilds, A.A.M., Coronell, R., 1986. Changes in conduction velocity during acute ischemia in ventricular myocardium of the isolated porcine heart. Circulation 1, 189–198.

Kline, R., Morad, M., 1976. Potassium efflux and accumulation in heart muscle. Biophys. J. 16, 367–372.

Kline, R.P., Morad, M., 1978. Potassium efflux in heart muscle during activity: Extracellular accumulation and its implications. J. Physiol. (London) 280, 537–558.

Knisley, S.B., Hill, B.C., 1995. Effects of bipolar point and line stimulation in anisotropic rabbit epicardium. IEEE Trans Biomed Eng 42, 957–966.

Knowles, W.D., Traub, R.D., Strowbridge, B.W., 1987. The initiation and spread of epileptiform bursts in the in vitro hippocampal slice. Neuroscience 21, 441–455.

Komuro, H., Sakai, T., Hirota, A., Kamino, K., 1986. Conduction pattern of excitation in the amphibian atrium assessed by multiple-site optical recording of action potentials. Jpn J Physiol 36, 123–137.

Kriebel, M.E., 1967. Conduction velocity and intracellular action potentials of the tunicate heart. J Gen Physiol. 50, 2097–2107.

Kriebel, M.E., 1969. Spread of excitation and injected current in the tunicate myocardium. In: McCann, F.V. (Ed.), Comparative Physiology of the Heart. Birkhäuser, Basel, pp. 111–134.

De Kruif, H.A.M., 1976a. The effect of electrical stimulation and some drugs on conducting systems of the hydrocoral *Millepora complanata*. In: Mackie, G.O. (Ed.), Coelenterate Ecology and Behavior. Plenum, New York, pp. 661–670.

De Kruif, H.A.M., 1976b. Spontaneous electrical activity and colonial organization in the hydrocoral *Millepora* (Milleporina, Coelenterata). Mar Behav Physiol 4, 137–159.

Kucera, J.P., Kléber, A.G., Rohr, S., 1998. Slow conduction in cardiac tissue, II: Effects of branching tissue geometry. Circ Res 83, 795–805.

Leys, S.P., Mackie, G.O., Meech, R.W., 1999. Impulse conduction in a sponge. J Exp Biol. 202, 1139–1150.

Lieberman, M., Paes De Carvalho, A., 1965. The spread of excitation in the embryonic chick heart. J Gen Physiol. 49, 365–379.

Lieberman, M., 1973. Electrophysiological studies of a synthetic strand of cardiac muscle. The Physiologist 16, 551–563.

Luo, C.-H., Rudy, Y., 1994a. A dynamic model of the cardiac action potential, I. Circ. Res. 74, 1071–1096.

Luo, C.-H., Rudy, Y., 1994b. A dynamic model of the cardiac action potential, II. Circ. Res. 74, 1097–1113.

Mackie, G.O., 1975. Neurobiology of Stomotoca. II: Pacemakers and conduction pathways. J Neurobiol. 6, 357–378.

Mackie, G.O., 1976. Propagated spikes and secretion in a coeoenterate glandular epithelium. J gen Physiol. 68, 313–325.
Mackie, G.O., 1978. Coordination in physonectid siphonophores. Mar Behav Physiol. 5, 325–346.
Mackie, G.O., Bone, Q., 1976. Skin impulses and locomotion in an ascidian tadpole. J mar biol Ass U.K. 56, 751–768.
Mackie, G.O., Bone, Q., 1977. Locomotion and propagated skin impulses in salps (tunicata: thaliaceae). Biol Bull. 153, 180–197.
Mackie, G.O., Meech, R.W., 1985. Seperate sodium and calcium spikes in the same axon. Nature 313, 791–793.
Mackie, G.O., Pasano, L.M., 1968. Epithelial conduction in hydromedusae. J. Gen. Physiol. 52, 600–621.
Mackie, G.O., Paul, D.H., Singla, C.M., Sleigh, M.A., Williams, D.E., 1974. Branchial innervation and ciliary control in the ascidian *Corella*. Proc R Soc Lond B 187, 1–35.
Mayer, A.G., 1914. The relation between the degree of concentration of the electrolytes of sea-water and the rate of nerve-conduction in Cassiopea Papers Tortugas. Lab Carnegie Inst 6 (119), 25–54.
Mayer, A.G., 1916. Nerve conduction, and other reactions in Cassiopea. Am J Physiol. 39, 375–393.
Mayer, A.G., 1917. Nerve-conduction in *Cassiopea xamachana*. Papers Dept Marine Biol Carnegie Inst. XI, 1–20.
McCann, F.V., 1971. Calcium action potentials in insect myocardial fibers. Comp Biochem Physiol 40A, 353–357.
McCann, F.V., 1964. Conduction in the moth myocardium. Comp Biochem Physiol 12, 117–123.
McFarlane, I.D., 1969. Two slow conduction systems in the sea anemone *Calliactis parasitica*. J Exp Biol 51, 377–385.
Morad, M., Cleeman, L., 1980. Tunicate heart as a possible model for the vertebrate heart. Federation Proc 39, 3188–3194.
Morin, J.G., Cooke, I.M., 1971. Behavioral physiology of the colonial hydroid. Obelia J Exp. Biol. 54, 689–706.
Muzikant, A.L., Henriquez, C.S., 1998. Validation of three-dimensional conduction models using experimental mapping: are we getting closer? Prog Biophys Mol Biol 69, 205–223.
Nicol, J.A.C., 1955. Nervous regulation of luminescence in the sea pansy *Renilla köllikeri*. J Exp Biol 32, 619–635.
Ohtsu, K., Yoshida, M., 1973. Electrical activities of the anthomedusan, *Spirocodon saltatrix* (Tileseius). Biol Bull 145, 532–547.
Olivo, O.M., 1948. L'elettrocardiogramma di espianti embrionali di miocardio coltivati esincronizzati "in vitro". Monit zool ital 56, 132–141.
Passano, L.M., McCullough, C.B., 1964. Co-ordinating systems and behavior in *Hydra* I. Pacemaker system of the periodic contractions. J exp Biol 41, 643–664.
Pearse, V., Pearse, J., Buchsbaum, M., Buchsbaum, R., 1987. Living Invertebrates. Pacific Grove, Boxwood.
Pertsov, A.M., Davidenko, J.M., Solomonz, R., Baxter, W.T., Jalife, J., 1993. Spiral waves of excitation underlie reentrant activity in isolated cardiac muscle. Circ Res 72, 631–650.
Pfitzner, I., 1962. Zur Bewegung von *Cestus veneris* Leseur (Ctenophora), eine Filmanalyse. Zool Jb Physiol 69, 577–598.
Pople, D.W., Ewer, E.W., 1954. Studies on the myoneural physiology of echinodermata. I. The pharyngeal retractor muscle of *Cucumaria*. J Exp Biol 31, 114–126.
Pople, D.W., Ewer, D.W., 1955. Studies on the myoneural physiology of echinodermata. I I. Circumoral conduction in *Cucumaria*. J Exp Biol 32, 59–69.
Prechtl, J.C., Cohen, L.B., Pesaran, B., Mitra, P.P., Kleinfeld, D., 1997. Visual stimuli induce waves of electrical activity in turtle cortex. Proc. Natl. Ac. Sc. USA 94, 7621–7626.
Prechtl, J.C., Bullock, T.H., Kleinfeld, D., 2000. Direct evidence for local oscillatory current sources and intracortical phase gradients in turtle visual cortex. Proc. Natl. Ac. Sc. USA 97, 877–892.
Prosser, C.L., Curtis, H.J., Travis, D.M., 1951. Action potentials from some invertebrate non-striated muscles. J Cell Comp Physiol 38, 299–319.
Prosser, C., Melton Jr, E., 1954. Nervous conduction in smooth muscle of *Phascolosoma* proboscis retractors. J Cell Comp Physiol 44, 255–275.
Prosser, C.L., Nystrom, R.A., Nagai, T., 1965. Electrical and mechanical activity in intestinal muscles of several invertebrate animals. Comp Biochem Physiol 14, 53–70.
Ridgway, E.B., Durham, A.C.H., 1976. Oscillations of calcium ion concentrations in *Physarum polycephalum*. J Cell Biol 69, 223–226.
Roberts, A., Stirling, C.A., 1971. The properties and propagation of a cardiac-like impulse in the skin of young tadpoles. Z vergl Physiologie 71, 295–310.
Roland, P.E., 2002. Dynamic depolarization fields in the cerebral cortex. Trends Neurosc. 25, 183–190.
Romanes, G.J., 1877. Further observations on the locomotor system of medusae. Phil Trans Roy Soc 167, 659–752.
Sakai, T., Fijii, S., Hirota, A., Kamino, K., 1983. Optical evidence for calcium-action potentials in early embryonic precontractile chick heart using a potential-sensitive dye. J Membrane Biol 72, 205–212.
Sandemann, D.C., 1965. Electrical activity in the radial nerve cord and ampullae of sea urchins. J Exp Biol 43, 247–256.
Satterlie, R.A., Anderson, P.A.V., Case, J., 1976. Morphology and electrophysiology of the through-conducting systems in pennatulid coelenterates. In: Mackie, G.O. (Ed.), Coelenterate Ecology and Behavior. Plenum, New York, pp. 619–627.
Sauer, H.W., 1982. Developmental Biology of *Physarum*. Cambridge University Press, Cambridge.
Sawanobori, T., Hirota, A., Fujii, S., Kamino, K., 1981. Optical recording of conducted action potential in heart muscle using a voltage-sensitive dye. Jpn J Physiol 36, 123–137.
Scherman, X?, Young, A.C., Malmgren, A.L., Paton, R.R., 1953. Spread of electrical activity through the wall of the ventricle. Circ Res 1, 539–547.
Schmandt, W., Sleator, W., 1955. Deviations from all-or-none behavior in a molluscan unstriated muscle: Decremental conduction and augmentation of action potentials. J Cell Comp Physiol 46, 439–473.
Sibaoka, T., 1958. Conduction of action potential in the plant cell. Trans. Bose Res. Inst. 22 (115), 43–56.
Sibaoka, T., 1966. Action potentials in plant organs. Symp Soc Exp Biol 20, 165–184.
Sleigh, M.A., 1968. Metachronal coordination of the comb plates of the ctenophore, *Pleurobrachia*. J Exp Biol 48, 111–125.
Smith, D.S., Brink, D., Del Castillo, X?, 1985. Nerves in the spine of a sea urchin. Proc Natl Acad Sci USA 82, 1555–1557.
Smits, A.W., Burggren, W.W., Oliveras, D., 2000. Developmental changes in *in vivo* cardiac performance in the moth *Manduca sexta*. J exp Biol 203, 369–378.
Spencer, A.N., 1971. Myoid conduction in the siphonophore *Nanomia*. Nature 233, 490–491.
Spencer, A.N., 1974. Behavior and electrical activity in the hydrozoan *Proboscidactyl flavicirrata* (Brandt) I. The hydroid colony. Biol Bull. 146, 100–115.
Spencer, A.N., 1978. Neurobiology of *Polyorchis*. I. Function of effector systems. J Neurobiol 9, 143–157.
Stevens, R.J., Publicover, N.G., Smith, T.H., 1999. Induction and organization of Ca^{2+} waves by enteric neural reflexes. Nature 399, 62–66.
Stokes, D.R., 1974. Physiological studies of conducting systems in the colonial hydroid *Hydractinia echinata*. J Exp Zool, 1–18 190.
Stuart, G.J., Sakmann, B., 1994. Active propagation of somatic action potentials into neocortical pyramidal cell dendrites. Nature 367, 69–72.
Stuart, G.J., Schiller, J., Sakmann, B., 1997. Calcium action potentials restricted to distal apical dendrites of rat neocortical pyramidal neurons. J Physiol (Lond.) 505, 617–632.
Sung, D., Omens, J.H., MCCulloch, A.D., 2000. Model-based analysis of optically mapped epicardial activation patterns and conduction velocity. Ann Biomed Eng 28, 1085–1092.
Sugi, H., 1960. Propagation of contraction in the stalk muscle of *Carchesium*. J. Fac. Sci. Univ. Tokyo IV–8, 603–615.
Taccardi, B., Macchi, E., Lux, R.L., Ershler, P.R., Spaggiari, S., Barrufi, S., Vyhmeister, Y., 1994. Effects of myocardial fiber direction on epicardial potentials. Circulation 90, 3076–3090.

Tasaki, I., Kamiya, N., 1950. Electrical response of a slime mold to mechanical and electrical stimuli. Protoplasma 39, 333–343.

Tenney, S.M., 1953. Observations on the physiology of the lepidopteran heart with special reference to reversal of the beat. Physiol Comp Oecol 3, 286–306.

Thomas, J.E., Schuessler, S.A., Berul, R., Beardslee, C.I., Beyer, E.C., Mendelsohn, M. E., Saffitz, J.E., 1998. Disparate effects of deficient expression of connexin43 on atrial and ventricular conduction. Circulation 97, 686–691.

Thorpe, J.P., 1982. Bryozoa. In: Shelton, G.A.B. (Ed.), Electrical Conduction and Behavior in 'Simple' Invertebrrates. Clarendon, Oxford, pp. 393–439.

Turner, R.S., Nevius, D.B., 1951. The organization of the nervous system of *Ariolimax columbianus*. J comp Neurol 94, 239–256.

Twarog, B.M., 1967. Excitation of *Mytilus* Smooth Muscle. J Physiol (London) 192, 857–868.

Verheule, S., Van Batenburg, C.A.J.A.C., Coenjaerts, X?, Kirchoff, S., Willecke, K., Jongsma, S., 1999. Cardiac conduction abnormalities in mice lacking the gap junction protein connexin 40. J Cardiovasc electrophysiol 10, 1380–1389.

Walrond, J.P., Stretton, A.O.W., 1985. Excitatory and inhibitory activity in the dorsal musculature of the nematode *Ascaris* evoked by single dorsal excitatory motoneurons. J Neuroscience 5, 16–22.

Weingart, R., 1977. The actions of ouabain on intercellular coupling and conduction velocity in mammalian ventricular muscle. J Physiol (London) 264, 341–365.

Weisblat, B.A., Russell, R.L., 1976. Propagation of electrical activity in the nerve cord and muscle syncytium of the nematode *Ascaris lumbricoides*. J comp Physiol 107, 293–307.

Weiss, J., Goldman, Y., Morad, M., 1976. Electromechanical properties of the single cell-layered heart of the tunicate *Boltenia ovifera* (sea potato). J Gen Physiol 68, 503–518.

Winfree, A.T., 1998. A spatial scale factor for electrophysiological models of myocardium. Prog Biophys Mol Biol 69, 185–203.

Yoshigi, M., Ettel, J.M., Keller, B.B., 1997. Developmental changes in flow-wave propagation velocity in embryonic chick vascular system. Am. J. Physiol. 273, H1523–H1529.