Review

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On the conservation of calcium wave speeds

Lionel F. Jaffe, Robbert Créton

Calcium Imaging Laboratory, Marine Biological Laboratory, Woods Hole, Massachusetts, USA

Summary Most long distance calcium signals are believed to take the form of actively propagated calcium waves. In 1991, when this proposal was first advanced, all such waves were thought to belong to one class, for which fertilization waves were the prototype. Moreover, the speeds of such waves were found to be conserved at about 10 μm/s for primary fertilization waves and 30 μm/s for waves through fully active systems at 20°C.

In 1993, preliminary evidence for a second class of such waves was published and the prototype for these were ones which drive cell cleavage. These move at only about 1 μm/s at 20°C and were, therefore, called **slow** calcium waves as opposed to the **fast** ones first considered. Here we compile compelling evidence that slow waves comprise a second distinct class of actively propagated calcium waves. This is based on 30 papers which yield evidence of slow calcium waves in organisms ranging from *Dictyostelium* to mammals and phenomena ranging from the surface contraction waves seen long ago in axolotl eggs to embryonic cleavage and mitotic waves and to ones recently seen to accompany primary neural induction in axolotls. **Ultraslow** and **ultrafast** calcium waves are also considered.

INTRODUCTION

In 1991, it was proposed that calcium signals generally take the form of actively propagated waves and that the speeds of such waves have been highly conserved over all of eukaryotic evolution [1]. This proposition was supported by the critical compilation of data from over 50 papers; data based upon images of free cytosolic calcium waves or of others, such as secretion or contraction, which could be attributed to calcium waves. Among these reports, the prototype was one on the fertilization wave through the medaka fish egg [2,3]. Since these reports included some evidence from organisms as primitive and diverse as sponges and of *Chara* – and surely extended through mammals – the observed constancy of wave speed was attributed to a conservation of wave speed over all of eukaryotic evolution. Moreover, since fast calcium waves are carried by the endoplasmic reticulum (ER), the conservation of speed must have arisen from a conservation of structure within the ER – an organelle believed to have been present from the beginnings of eukaryotic evolution and never lost.

Then, in 1993, one of us published a preliminary compilation of evidence for a second, distinct class of far slower calcium waves which was likewise thought to be carried by the ER [4]. Here, we greatly extend this compilation and thus better show the existence of a distinct class of slow calcium waves.

While the conservation of fast wave speeds that was proposed in 1991 has never been contested in print [5], one substantial exception has privately troubled investigators of calcium signals: namely, the anomalously high speed of calcium waves through so-called cardiomyocytes, tissue culture cells obtained from heart fragments. Here we note a recent publication [6] which establishes that calcium waves through whole hearts, as opposed to cultured heart fragments, do move at the conserved fast

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Correspondence to: Calcium Imaging Laboratory, Marine Biological Laboratory, 7 MBL Street, Woods Hole, MA 02543, USA
Tel: +1 508 289 7251; Fax: +1 508 540 6902
E-mail: ljaffe@mbl.edu

Abbreviations: ER, endoplasmic reticulum; SCW, surface contraction wave; sd, Leao's spreading depression.

Table 1 Slow calcium wave speeds. Of the 30 listed cases, only the 5 indicated by aequorin are ones in which calcium waves were imaged; in the other 25 cases they are predicted. OD means optical density

No.	Organism	Stage/Process	Indicator	T (°C)	μm/s	Year	Ref.
Eggs							
1a	Axolotl	Precleavage	Contraction	21	0.5	1971	[14]
1b	*Xenopus*	Postfertilization	Contraction	24	0.65	1977	[15]
1c	*Xenopus*	Precleavage	Contraction	24	1.1	1977	[15]
1d	*Xenopus*	Precleavage	Contraction	22	0.9	1977	[15]
1e[a]	*Xenopus*	Precleavage	Contraction	21	1.0	1980	[16]
1f[b]	*Xenopus*	Precleavage	Contraction	20	0.5	1993	[17]
1g	Newt	Precleavage	Contraction	22	0.8	1982	[18]
1h	Newt	Precleavage	Contraction	Room	0.5	1982	[19]
2	Barnacle	Precleavage	Contraction	14	0.3	1973	[20]
3	Ascidian	Precleavage	Contraction	24	1.0	1989	[21]
4	*Beröe*	Precleavage	Movement	15	0.25	1993	[22]
5[c]	Urchin	Precleavage	**Aequorin**	Room	1.5	1996	[23]
6	Cnidarian	Cleavage	Furrowing	12.5	0.17	1947	[24]
7	*Xenopus*	Cleavage	**Aequorin**	Room	0.5	1990	[25]
8a	Medaka	Cleavage	**Aequorin**	Room	0.6	1991	[26]
8b	Zebrafish	Cleavage	**Aequorin**	28	0.5[d]	1997	[27]
8c	Zebrafish	Cleavage	**Aequorin**	27	0.5	1998	[28]
Early multicellular stages							
10a	Blowfly	9–12 mitoses	Anaphase	20	0.8	1963	[29]
10c	Midge	1–4 mitoses	Mitosis	23	0.4	1988	[30]
10d	*Pimpla*	8–10 mitoses	Mitosis	21	0.4	1988	[30]
10e	*Drosophila*	10–13 mitoses	Mitosis	25	2?	1988	[31,32]
11a	Axolotl	9–13 mitoses	Mitosis	21	1.3	1977	[33]
11b	Axolotl	5–13 mitoses	Mitosis	22	1.2	1977	[34]
Later developmental stages							
12a	*D. discoideum*	Close packed	OD	Room	0.7	1965	[35,36]
12b	*D. discoideum*	Mounds	OD	21	1.5	1996	[36,37]
12c	*D. discoideum*	Slugs	OD	21	1.0	1996	[36,37]
13	Insect	Anatrepsis		23	0.6	1972	[38]
14	Chick	Gastrulation	Pulse start	37.4	3.3	1977	[39]
15	Chick	Stage 12	Refraction	38	3.4	1979	[40]
16	Axolotl	Neural induction	OD	20	0.14[e]	1994	[41]
17	Hydroid polyps		Waves of cell rotation	17–18	0.5–1.1	1989	[73]

[a]These eggs were prick-activated and did not cleave. Yet, 5 or 6 pairs of surface contraction waves moved as they would have had 5 or 6 cleavages occurred.
[b]Unlike SCWS, these were obtained from movements of vegetal germ plasm markers.
[c]Centripetal waves of relatively uncertain speed.
[d]A figure of 0.2 rather than 0.5 μm/s was published; however, this arose from a computer error (E. Karplus, personal communication).
[e]Peripheral speed taken from images published in [41] to be 0.1 μm/s and raised 40% on the assumption that the wave spread up the forward edge of the furrow. A further discussion can be found in reference [42].

calcium wave rate. Moreover, a number of new or of reconsidered reports of fast waves, particularly ones of calcium [7] and of Leão's spreading depression [8] through isolated retinas and of spreading depression in the brains of anesthetized rabbits [9] or rats [10], have convinced us that spreading depression is driven by fast calcium waves. They also support Lauritzen's proposal that spreading depression within the brain's visual cortex underlies migraine [11,12] and the proposal that fast calcium waves (Leibowitz's cytocal waves) underlie both spreading depression [1] and migraine [4,12].

SLOW CALCIUM WAVES

Velocity conservation

Table 1 and Figure 1A present the compilation of data which establish a well defined class of slow waves with speeds that are conserved over a range of about 10-fold at a given temperature. Of the 30 cases shown, only 5 are waves of imaged, high, cytosolic calcium. We predict that the other 25 will prove to be such waves because the phenomena observed – particularly ones of localized

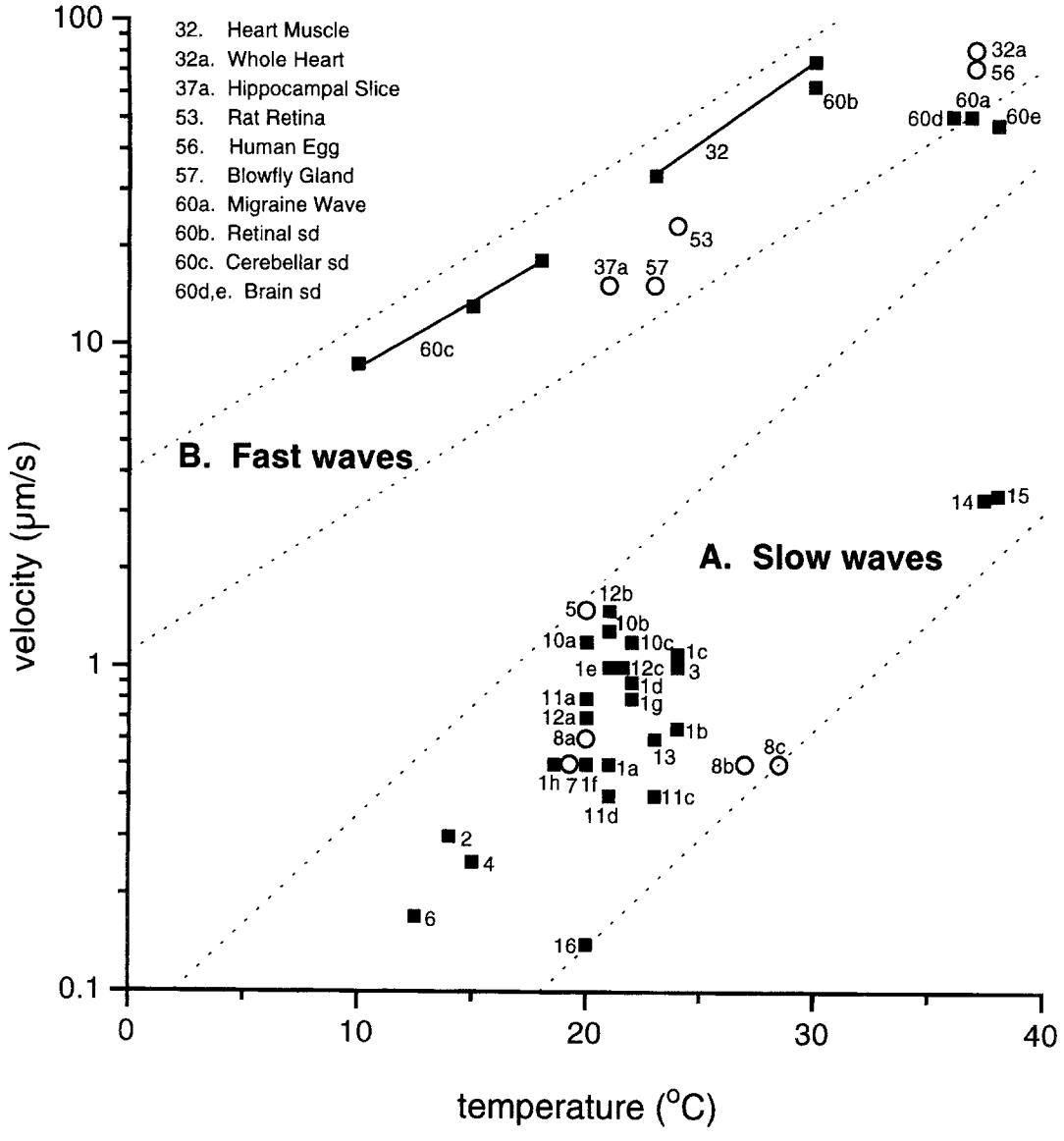

Fig 1 Data showing the conservation of calcium wave speeds. Open circles indicate cases where calcium waves were imaged; filled circles indicate ones where they are predicted. (**A**) Slow wave data taken from Table 1. The envelope was chosen to minimize the range of data across it. (**B**) Fast wave data show some particularly interesting cases taken from Table 2. Note that the whole heart as well as heart muscle data fall within the conserved range. This envelope was chosen to minimize the range of the 67 data points for fully active systems tabulated in [1,4] and Table 2. [***Note***: The data given in Tables 1 and 2 relating to references 67–73 were added to the page proofs and are not included in the above figure.]

contraction – are so likely to be driven by localized increases in $[Ca^{2+}]_i$.

These 30 cases fall into 4 main groups of phenomena. Cases 1–4 and 16 seem to arise from slowly moving rings of surface contraction of the sort first reported by Hara in a 1971 study of axolotl eggs [14] and by Lewis et al. in a 1973 study of barnacle eggs [20]. Indeed, Hara called them surface contraction waves (SCWs) while Lewis et al. called them peristaltic contractions. It is interesting that the recently reported SCW during neural induction, like Hara's waves, was seen in living axolotl embryos as a wave of optical density increase. However, sections of fixed embryos leave no doubt that it is indeed a wave of gross surface contraction [41]. Moreover, in the largely forgotten early study of barnacle zygotes, the waves of 'peristaltic constriction' could be clearly seen to be waves of gross surface contraction in living, normally developing embryos [20].

Table 2 New, newly compiled or reconsidered fast calcium wave speeds in fully active systems[a]

No.	Group	Genus/system	Indicator	T (°C)	μm/s	Year	Ref.
32	Mammals	Rat heart muscle	Phase contrast	23	33	1985	[45]
32	Mammals	Rat heart muscle	Phase contrast	30	74	1985	[45]
32a	Mammals	Whole rat heart	Fluo–3/AM	37	80	1997	[6]
37a	Mammals	Hippocampal slices	Fluo–3/AM	21	15	1992	[46]
44a	Mammals	Mouse myotubes	Fluo–3/AM	24	35	1993	[47]
44b	Birds	Chick myotubes	Fluo–3/AM	24	70	1993	[47]
53	Mammals	Rat retina	Ca-Green/AM	24	23	1997	[7]
54	Nemerteans	Zygote	Dextranned	14	16–32[b]	1996	[48]
55	Birds	Streak stage	Pulsing	37	33	1977	[39]
56	Human	Sperm injected egg	Fluo–3/AM	37	75[c]	1994	[49]
57	Insect	Blowfly salivary	Fura–2/AM	23	15	1997	[50]
58	Mammals	Neuroblastoma	AM esters	37?	33	1996	[51]
59	Mammals	Megakaryocyte	Fura–2/AM	Room	34	1997	[52]
60a	Human	Brain sd	Scotoma	37	50	1941	[53]
60b	Birds	Retinal sd	Scattered light	30	62	1974	[8]
60c	Elasmobranch	Cerebellar sd	Electrical	10	8.6	1980	[54]
60c	Elasmobranch	Cerebellar sd	Electrical	15	13	1980	[54]
60c	Elasmobranch	Cerebellar sd	Electrical	18	18	1980	[54]
60d	Mammal	Brain sd	Electrical	33	50	1994	[9]
60e	Mammal	Brain sd	Laser-Doppler	38?	47	1995	[10]
60f	Mammal	Brain slice sd	Fura–2/AM	33	30–50	1997[d]	
60g	Rat	Brain slice sd	Fluo–3/AM	37	67	1998	[67]
61a	Ferrets	Developing retinas	Voltage waves	31–34	150–300	1993	[68]
61b	Ferrets	Developing retinas	Voltage waves	36±1	100–300	1997	[69]
62	Rat	Whole liver	Rhod–2/AM	37	33	1995	[70, Fig.2]
63	Rat	Hepatocytes	Fura–3/AM	37	49[e], 77[f]	1997	[71]
64	Bovine	Endothelial cells	Indo–1/AM	23	30±1	1998	[72]

[a]Cases #1–44 are in [1] while 45–52 are in [4].
[b]Speed along the surface.
[c]Our estimate from Figure 3.
[d]Unpublished data of B.A. MacVicar.
[e]Through the nuclei
[f]Around the nuclei
sd= spreading depression.

We are led by this overview to rebut two recent assertions that Hara's first precleavage SCW in *Xenopus* [16] is anomalous; that it is a wave of surface expansion rather than one of surface contraction [43,44]. These assertions rest heavily on a 1982 paper by Yoneda et al. [18] which strongly disputes Hara's description of SCW-1 as a contraction rather than a relaxation wave. However, the rest of the Yoneda et al. paper provides practically no support for this contention: it does not report any effort to repeat Hara's basic time lapse observations of whole, normally developing axolotl and *Xenopus* eggs and the only data indicative of local stretching is in Yoneda et al.'s Figure 8. This figure does indicate a wave of surface particle separation which preceded one of particle aggregation in one newt egg; however, we would take the conservative view that this separation was the passive consequence of nearby active surface contraction. Particular because active, actinomyosin-based, local, surface contraction is a widespread phenomena in living cells; yet, to our knowledge, nothing is yet known of such relaxation phenomena.

The second large group of slow calcium phenomena are ones of cleavage furrow elongation as listed in cases 6–8. These seem very similar to the first group except that the observed waves of surface contraction spread in one dimension instead of two. Moreover, observations of the accompanying calcium wave are largely restricted to this group. We would predict that all normally elongating, cleavage furrows or contractile arcs will prove to elongate within the same range of speeds at a given temperature as do other slow waves.

The third large group are the waves of early asynchronous mitosis initiation or of the subsequent asynchronous cleavage initiation listed in cases 10,11. Such mitotic wave speeds typically slow down – perhaps as other constraints come into play. While such mitotic waves are not surface contraction waves, they are accompanied by them [30,32]. Moreover, like cleavage waves [26], they are certainly properties of 'excitable media' in the sense that they are readily initiated ectopically and thus caused to propagate opposite to their natural direction [30–32].

The fourth are the waves of intra-organismic optical density or refractive index change listed in cases 12 (multicellular stages of *D. discoideum*) and 15 (advanced chick embryos). It is true that the remarkable optical density waves seen in *D. discoideum* have been generally believed to be extensions to multicellular stages of the famous, cAMP propagated aggregation waves. However, it has been recently argued that they are actually slow calcium waves that, like others in this class, are propagated by mechanical tension rather than molecular or ionic diffusion [36].

FAST CALCIUM WAVES

Table 2 further updates data on fast calcium wave speeds while Figure 1B shows some particularly interesting cases that are taken from this table and placed within an envelope of the accumulated 59 data points for fully active systems (exclusive of the tiny, artificial cells obtained from heart fragments).

Case 32a shows the recently measured speed of calcium waves through whole rat hearts. As noted in the introduction, this new finding is of particular interest, since it explains the main anomalous calcium wave speeds found in previous compilations. Cultured heart fragments, or cardiomyocytes do exhibit calcium waves which move at about 3 times the otherwise conserved rate, but calcium waves through whole hearts move at the conserved rate [6]. Moreover, old observations of contractile wave speeds through isolated heart muscle – assumed to be calcium wave speeds – likewise showed speeds in the conserved range [45]. So the conservation of fast calcium wave speeds now seems to be rather well established. While fully meaningful exceptions to fast wave conservation are no longer available, there does seem to be an interesting exception to the idea that all natural, whole cell calcium oscillations take the form of calcium waves. Observations of free cytosolic calcium within fully grown (but immature) mouse oocytes show highly repetitive oscillations which take the form of global, synchronous $[Ca^{2+}]_i$ increases throughout the cell [55]. Perhaps these repetitive calcium oscillations in oocytes do begin as waves but are later synchronized by the kinds of phenomena which synchronize coupled oscillators in the heart, pancreas and brain [56].

Case 60 presents relatively accurate data on the speed of Leão's spreading depression since we have become convinced that such waves are driven by fast calcium waves. In part, we are convinced by the very fact that such data lie well within the rather narrow envelope of fast calcium wave data. The speeds reported in old observations of spreading depression within the molecular layer of the cerebella of whole anesthetized skates are particularly convincing here [54]. Note that even the temperature dependence of these data has the same low value known to be characteristic of fast calcium waves. The speed of even older observations of spreading depression within isolated chick retinas seem to be exceptionally accurate, since they continued at steady rates for 30 revolutions round the retina over 3–4 h! [8]. However, the striking calcium waves recently reported to move around acutely isolated rat retinas by Newman and Zahs likewise move at this same highly conserved velocity [7] but were not accompanied by spreading depression (E. Newman, personal communication). What are we to deduce from this? Certainly not that isolated rat retinas cannot propagate spreading depression waves under appropriate conditions. Rather that some obscure aspect of Newman and Zahs' conditions allowed fast calcium waves without allowing spreading depression. Thus we would infer that fast calcium waves are necessary, but not sufficient, to support spreading depression waves and, indeed, propose that they drive them.

Moreover, an interesting medical aspect is provided by Lashley's remarkable 1941 inference of the speed of injury waves within his own visual cortex during his own migraine attacks [53], together with relatively recent observations of the speeds of spreading depression within the brains of anesthetized mammals [9,10] and of calcium waves through the astrocytes of a rat's hippocampal slice [46]. These data should revive Lauritzen's well argued case for 'cortical spreading depression as a putative migraine mechanism' [11,12] and support the hypothesis that cortical spreading depression is driven by a fast calcium wave. So does the well known efficacy of beta blockers in preventing migraine.

Figure 1 also shows that the range of fast calcium wave speeds is far below that of slow ones and suggests that the temperature dependence of fast waves is likewise well below that of slow ones. Both of these matters presumably arise from the fact that fast calcium waves (unlike slow ones) are reaction diffusion waves whose velocity depends upon the square root rather than the first power of the rate limiting chemical reaction [1]. Indeed, this square root dependence predicts that the both the range at a given temperature and the Q_{10} of fast waves should approximate the square root of these values for slow ones. In fact, in the semilog plot of Figure 1, the fast wave speed range at a given temperature is 46% of the slow wave one compared to the 50% expected; while the fast wave Q_{10} is about 70% of the slow wave Q_{10} compared to the 50% expected. We would tentatively attribute the large size of this last discrepancy to the gross inaccuracy involved in estimating the Q_{10} of slow wave speeds from a comparison of data from many systems rather than a measurement of the Q_{10}s of individual ones.

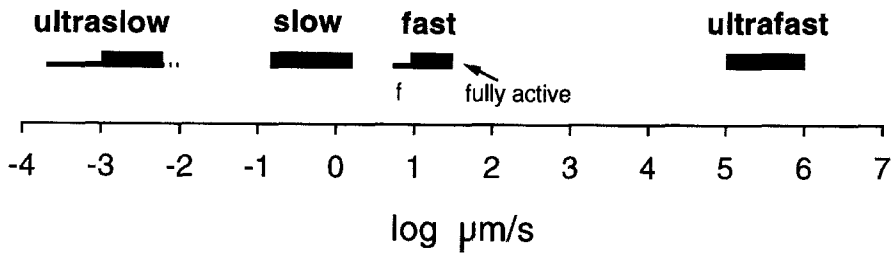

Fig. 2 Classes of calcium wave speeds at room temperature. Note how narrow the ranges of fast and slow calcium waves are when seen in this larger context. f = fertilization waves. Ultrafast means calcium driven action potentials; ultraslow means various developmental waves such as the morphogenetic furrow in *Drosophila* eye discs.

DISCUSSION

We submit that the conservation of fast and of slow wave speeds is now well established. It is true that only a minority of the 100 or so cases which support this conclusion have been shown to be calcium waves. However, we predict that the rest will all prove to be. Moreover, data are emerging to support two other distinct classes of propagated biological waves with conserved speeds. As Figure 2 shows, these include ultraslow ones traveling at about 1–100 nm/s and ultrafast ones traveling at about 0.1–1 m/s.

By ultraslow waves, we refer to developmental waves which are far slower than slow ones yet can be induced ectopically, can be induced to move backwards and can, therefore, be inferred to traverse what physical chemists call excitable media [57]. Moreover, they are accompanied by evidence of gross local contraction and can, therefore, be inferred to be calcium waves. Among these are ones which underlie progress of the morphogenetic furrow in developing *Drosophila* eye discs [58,59], which underlie progress of the DNA replication band through the macronuclei of ciliated protozoa [60] and which underlie the progress of growth-cone-like processes along the axons of isolated, embryonic, hippocampal neurons [61]. The evidence for these and other ultraslow waves is assembled and discussed elsewhere [62].

By ultrafast calcium waves, we refer to those action potentials which require an influx of calcium ions to be propagated under natural conditions. There is evidence that such action potentials generally occur in the early stages of nerve cell development [63,64]. However, we only know of two cases in which the speeds of calcium dependent action potentials have been measured. Namely, a speed of 0.25 m/s at 10–13°C for calcium spikes through a mature jellyfish [65] and one of 0.5 m/s through dendritic regions of cells in embryonic rat brain slices at 35°C [66]. Such ultrafast waves are calcium ones by definition but the conservation of their speeds is far from established. Two swallows do not make a spring! Nevertheless, we would point out that ultrafast waves are electrically propagated between relay points in contrast to fast ones which are propagated by calcium diffusion between such points and to slow ones which seem to be mechanically propagated between such points.

Finally, one may ask what mechanisms have conserved the speeds of three or four classes of putative calcium waves over so much of evolution. We would suggest that the conservation of fast, of slow and of ultraslow wave speeds occurred because they are all properties of multiprotein machines within the ER that are too complex and too vital to change after the ER's invention. Thus it may have arisen through the same broad mechanism that seems to have conserved the rates of protein synthesis per ribosome over all of eukaryotic evolution.

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