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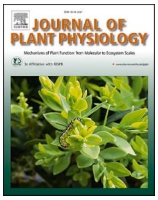

Opinion

Plants have neither synapses nor a nervous system

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ABSTRACT

The alleged existence of so-called synapses or equivalent structures in plants provided the basis for the concept of Plant Neurobiology (Baluska et al., 2005; Brenner et al., 2006). More recently, supporters of this controversial theory have even speculated that the phloem acts as a kind of nerve system serving long distance electrical signaling (Mediano et al., 2021; Baluska and Mancuso, 2021). In this review we have critically examined the literature cited by these authors and arrive at a completely different conclusion. Plants do not have any structures resembling animal synapses (neither chemical nor electrical). While they certainly do have complex cell contacts and signaling mechanisms, none of these structures provides a basis for neuronal-like synaptic transmission. Likewise, the phloem is undoubtedly a conduit for the propagation of electrical signaling, but the characteristics of this process are in no way comparable to the events underlying information processing in neuronal networks. This has obvious implications in regard to far-going speculations into the realms of cognition, sentience and consciousness.

1. Introduction

As a new hypothesis, Plant Neurobiology (PN) came to life in the years 2005/6 (Baluska et al., 2005; Brenner et al., 2006). The originators claimed that plants had synapse equivalents suggesting a similarity to neurons with neurotransmitter release via synaptic vesicles. Although evidence in this regard was not forthcoming, and despite numerous refutals over the years (Alpi et al., 2007; Taiz et al., 2019, 2020; Mallatt et al., 2020, 2021; Draguhn et al., 2020), supporters of the PN concept continue to refer to “synaptic-like domains“, as most recently in Baluska and Yokawa (2021) and Baluska and Mancuso (2021). Likewise, speculations have been made that would have the phloem acting as a kind of nerve system serving long distance electrical signaling (Mediano et al., 2021; Baluska and Manusco, 2021). In order to illustrate the use of terms and arguments in the respective literature we cite two passages from the recent papers of Baluska and Mancuso (2021) and Mediano et al. (2021):

1. *The plant-specific F-actin/myosin VIII-based synapse-like cell–cell adhesion domains in root apices, where synaptic-like principles were first proposed and characterized some 15 years ago [*Baluska et al., 2000*;* Baluska and Mancuso, 2013b*;* Kwon et al., 2008*;* Lima et al., 2009*], are active in the unique root apex zone known as the root apex transition zone [*Baluska et al., 2010*;* Baluska and Mancuso, 2013a*]. However, the plant-specific synaptic-like domains in the epidermis, endodermis and pericycle, as well as the vascular parenchyma lining vascular elements, support APs and integrate the whole plant body into a coherent unit, enabling plant-specific cognition and sociality (*Baluska and Mancuso, 2021*).*
2. *Propagation of electric signals takes place in the membranes of plant cells, running along the vascular system such that appropriate action can be taken (*Pickard, 1973*). We may thus interpret plant vasculature as a (neural-like) network of sieve tube elements in which the individual cells, interconnected* via *such vascular strands, furnish the computational building blocks (*Baluška et al., 2006*;* Bassel, 2018*) – akin to neurons and axons taking part in more complex animal brains. (*Mediano et al., 2021*).*

In this article we have critically examined the claims for the existence of synapses and nerves as a structural and physiological basis for nervous system-like information processing in plants. We conclude in both cases that there is no hard scientific evidence in favor of these speculations.

2. Plant synapses: what are they really?

Let us carefully examine the evidence in favor of plant synapses and ask whether they are present in the meristem-transition zone region of

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the root which is where supporters of the PN concept maintain that a kind of brain or control center for electrical signaling exists (Baluska et al., 2004, 2009).

2.1. But first, what are the salient features of synapses in animals?

Synapses are specialized contact zones between sub-cellular domains of two neurons or between a neuron and a sensory or an effector (muscle or glandular) cell. They mediate precisely confined signals between these cells which is a key prerequisite for information processing in neuronal networks. The term “synapse” was first introduced by Sir Charles Sherrington in a textbook of physiology (Foster, 1897). By joining the Greek words σύν (“*syn”,* together) and ἅπτειν (“*haptein”* to fasten) he emphasized the key function of this junction, namely to provide a nexus for signal conduction in spinal reflex arcs of animals (Sherrington, 1906; Burke, 2007). This concept was embedded in the “neurone doctrine”, stating that the nervous system consists of isolated cells that are surrounded by a plasma membrane, irrespective of their highly complex form and tight contacts. The neurone doctrine, prominently defended by Santiago Ramón y Cajal, was opposed to the “reticular theory“ of Camillo Golgi and others who held that the nervous system is a plasma-continuous network or syncytium (Golgi, 1906; Ramon y Cajal, 1906). Final proof for the neuron doctrine came from direct observations of membranes at neuronal contacts by electron microscopy in the mid-twentieth century (Palay and Palade, 1955; de Robertis and Bennett, 1955).

Synapses occur in two structurally and functionally highly specialized forms, one mediating signals by chemical transmission (neurotransmitters) and the other by direct electrical communication. We summarize core features of both types, beginning with electrical synapses. These structures are usually called “gap junctions“ due to the ultrastructurally visible separation of two cell membranes despite their close apposition (see Fig. 1 a). In mammals, they are formed by hexameric connexin channels in two cells which bind to each other, forming a continuous connection between both cytoplasms (Fig. 1 b) (Hervé and Derangeon, 2013; Szczupak, 2016). Gap junctions are permeable to ions and small molecules, including second messengers like cAMP. The diffusion of small molecules via gap junctions is sometimes described as a partial success of the reticularist position, but it should be kept in mind that gap junctions have a limited pore diameter, preventing the exchange of

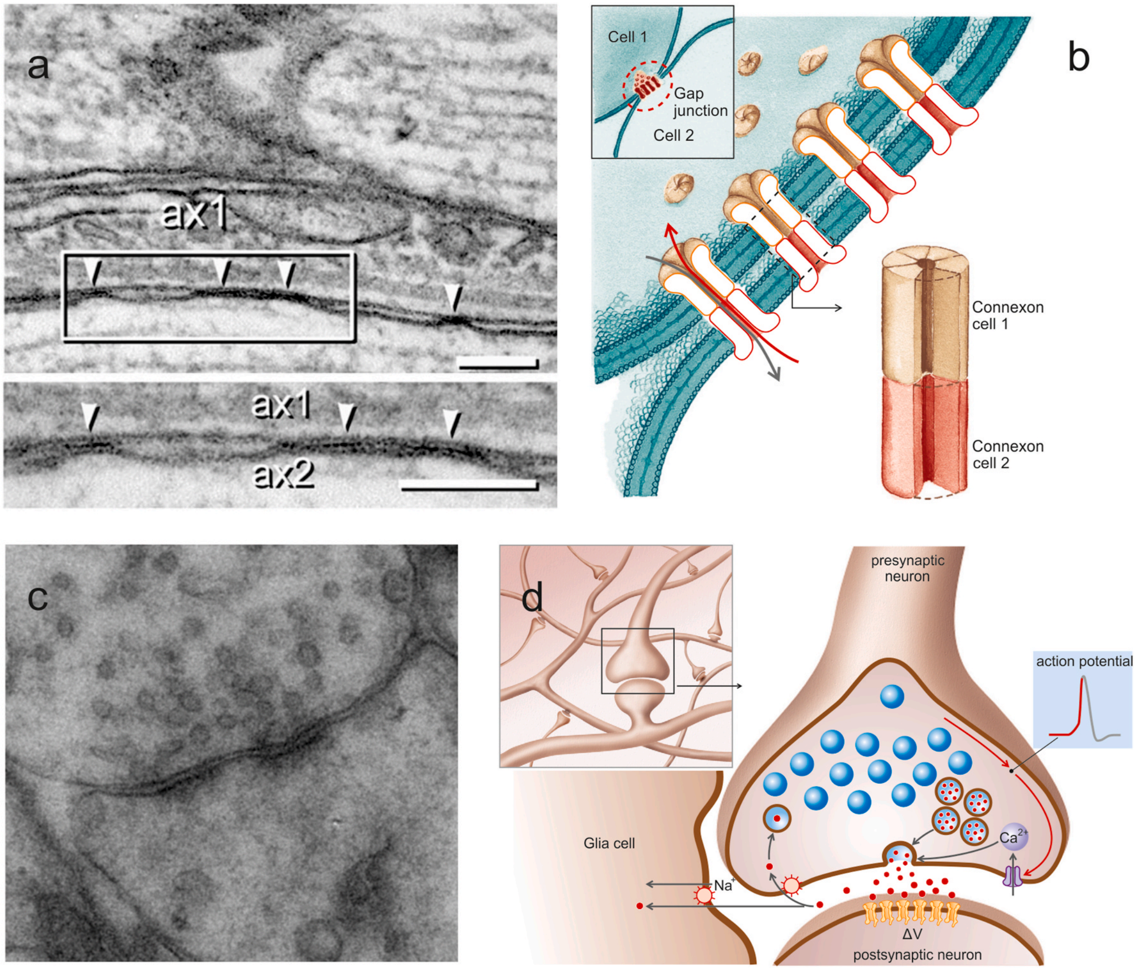

Fig. 1. Basic Features of Synapses.
Electrical synapses or gap junctions (a). Electron micrograph of a gap junction between two axons in the rat hippocampus (labeled ax1 and ax2, respectively). Note the close apposition of both membranes at the electrical synapse. (From Hamzei-Sichani et al., 2007). The molecular composition of gap junctions is illustrated in (b). The intracellular space of two cells is connected by two hemi-channels (connexons) which are each assembled from six connexin subunits. As a result, ionic currents and small molecules can pass between both cells. Chemical synapse in cultured rodent neurons (c). Note the asymmetric structure with transmitter-filled vesicles in the presynaptic terminal (upper part of the panel) and a visible specialization of the postsynaptic membrane (postsynaptic density). (Courtesy of Dr. Bernd Heimrich). (d) Schematic representation of a synapse within a neuronal network (inset). Transmitter-filled vesicles are released upon propagation of an action potential into the presynaptic terminal. Transmitter molecules (red dots) bind to postsynaptic receptors and elicit a defined electrical response (postsynaptic potential, indicated as ΔV). (Graphical illustrations from Rüdiger Gay).

proteins. For the same reason they constitute a considerable electrical resistance which leads to strongly attenuated electrical signal amplitudes in the coupled cell. Most gap junctions are non-rectifying, i.e. they conduct currents in both directions, in sharp contrast to chemical synapses. In vertebrate nervous systems they are the exception, rather than the rule, and appear to have evolved later than chemical synapses, probably by neo-functionalization of cell contacts mediating exchange of metabolites (Ovsepian, 2017). Electrical synapses in non-vertebrates depend on different sets of molecules, called innexins or pannexins, and are more frequent (Szczupak, 2016). Importantly, gap junctions are in no way confined to nervous systems. In mammals, including humans, they mediate the propagation of electrical activity in the heart, in large portions of smooth musculature and are present in different epithelia and parenchymas, e.g. in the liver. Thus, electrical signal propagation between cells is no marker of nervous systems. In fact, electrical signal transmission can also occur without specialized structures like gap junctions, e.g. by direct electrical interactions across membranes (ephaptic transmission) or by larger physical connections (nanotubes).

The most frequent neuronal connection is, however, the chemical synapse (Fig. 1 c,d). These structures use the release of transmitter molecules from a specialized presynaptic element (typically an axon ending) which elicits a defined reaction in the immediately adjacent postsynaptic element (typically a specialized membrane region of a dendrite or cell body). Therefore, chemical synapses are rectifying, i.e. supporting unidirectional signal flow from the pre-to the postsynaptic cell. A second important feature is their strictly confined effect, both in time and in space. Transmitter molecules are rapidly inactivated or removed after release, such that their interaction with the postsynaptic membrane is short-lasting and highly regional (often in a range of few ms and less than one μm). Synapses support fast input-output reactions, e.g. in sensory-motor reflexes, as already noted by Sherrington (1906). They are generally needed to coordinate multicellular activity in metazoan animals (Jékely et al., 2015). With this, they enable locomotion, targeted cue responses, food processing, reproductive behavior and other functions of animals, including the complex neuronal network activity supporting cognition (see below).

Chemical synapses occur in three of the five clades of metazoan animals (ctenophora, cnidaria, bilateralia), but not in placozoa and porifera. Interestingly, the latter possess much of the molecular machinery underlying synapses, raising the possibility that they lost their pre-existing nervous system during evolution (Ryan and Chiodin, 2015; Moroz and Kohn, 2016; Ovsepian, 2017). Many molecular constituents of synapses like ion channels, SNARE complexes and cell adhesion molecules are widely found in multiple cell types and across all organisms, including protozoa, bacteria and plants (Miller, 2009; Plattner and Verkhratsky, 2018; Elliott et al., 2020). This has led to the hypothesis that synaptic transmission evolved out of general intercellular communication mechanisms like paracrine signaling which were already present in early metazoan organisms (Miller, 2009; Varoqueaux and Fasshauer, 2017). In any case, the precision, speed, rectification and structural complexity of chemical synapses are unique features of neurons and their connected sensory or muscle/glandular cells. Hence, the concept should be clearly distinguished from metaphorical uses of the word like the „immunological synapse“, a transient connection between T- and B-lymphocytes (Shepherd and Erulkar, 1997).

Therefore we must now ask whether plants have distinct domains which correspond to neuronal synapses, e.g. “hot spots“ in the plasma membrane for vesicle fusion and for electrical signaling? Of the papers cited by Baluska and Mancuso (2021) in support of the existence of synapses in plants (see above) all refer to situations where there is an interaction between parasites and host plant cells. None of these cases is seen in the meristem-transition region of the root, but rather in the cortex of the root elongation zone (mycorhiza/symbiotic bacteria) or in leaf mesophyll (invading fungal pathogens). Whether a beneficial or defense situation, the plant host cell reacts to the foreign organism by intense, highly localized secretory activity involving both Golgi-derived vesicles carrying pectins and callose synthase (Kwon et al., 2008; Voigt, 2014) as well as the release of “exosomes“, through fusion of multivesicular bodies with the host cell plasma membrane (Robinson, 2015; Roth et al., 2019). These structures are quite unlike animal synapses both in structure and function. Nor is there any evidence to suggest that these interacting plasma membrane domains are hot spots of electrical signaling, although it has been proposed for the so-called “symbiotic synapse” in root nodules that an electrochemical gradient is created across the opposing plasma membranes that fuels the secondary transport of P_i, sucrose etc. (Lima et al., 2009). Perhaps this is the reason why the originators of the plant synapse concept refer to these structures in general as “immmunological plant synapses“ to distinguish them from the chemical or electrical synapses of animals (Baluska et al., 2005). Despite this clear distinction, plant neurobiologists have gradually mutated the term “plant synapse“ to include electrical signaling properties in the sense of a chemical synapse in neurons. This is an assumption for which there is no scientific foundation.

Another term that plant neurobiologists have appropriated from the animal literature is “adhesive contacts“, which is a misnomer since direct contact between plant cells, and therefore adhesion of adjacent plasma membranes is not possible due to the cell wall. Nevertheless, Baluska et al. (2005) consider the non-growing cross walls lying between elongating plant cells to be “adhesive domains“ which, in turn, are described by them to be a “plant developmental synapse”. Characteristic of the cortical cytoplasm in the region of the cross walls are F-actin and the plant-specific class VIII myosin (Baluska et al., 2000). We assume therefore (since references are not given) that when Baluska and Mancuso (2021) write “*plant-specific synaptic-like domains exist in the epidermis, endodermis and pericycle, as well as the vascular parenchyma lining vascular elements*“ they are referring to specific actin-myosin domains that are visible in the confocal microscope. Evidence for intensified vesicle fusion with the plasma membrane at these sites has not been presented, and certainly there is no indication that these loci are preferred sites for action potential generation and propagation.

Supporters of the PN concept have also proposed that, in analogy to neurotransmitters in the chemical synapse of animals, the hormone auxin selectively accumulates in secretory vesicles which then fuse with the plasma membrane (Baluska et al., 2010; Baluska and Mancuso, 2013b). While accepting that in order to exit the cytoplasm transmembrane transport complexes are required (the PIN-family of auxin transporters, Zwiewka et al., 2019) plant neurobiologists have assumed that these are already active in secretory vesicles. This speculation has however been solidly disproved experimentally (Robinson et al., 2018) and finds no support in calculations based on the distribution of the PIN-family of auxin transporters (Hille et al., 2018). Although these auxin transporters are subjected to a continual recycling between endosomes and particularly the plasma membrane of the cross walls (Adamowski and Friml, 2015) as far as we are aware, this process does not contribute to voltage changes at the plasma membrane.

An interesting example for overspeculation in terms of “similarities“ between signaling in phloem and neurons involves glutamate and GABA (gamma-aminobutyric acid) receptors. Glutamate and GABA are well-known neurotransmitters. Both amino acids are found in the phloem and it has been shown that glutamate acts as a wound signal (Toyota et al., 2019), although it is unclear whether glutamate/GABA are transported over long-distances in the phloem (Ramesh et al., 2017), or only restricted to the wound areas. Plants have several glutamate receptor (*GLR)* genes that are homologous to their animal counterparts (Mousavi et al., 2013) and double mutants show a weakened response to herbivore-induced wound signaling (Nguyen et al., 2018; Toyota et al., 2018). If GLRs in plants were to act as pendants to their neuronal counterparts one would expect them to be located to the PM, perhaps even clustered as in animal synapses. But there is as yet limited evidence for this. As documented in the paper of Nguyen et al. (2018) GLR-Venus fusion proteins are detected mainly in the ER and in the vacuole. This indicates that GLR proteins, being gated ion channels, may well be acting to control Ca^{2+} release from endomembrane sources as previously suggested by studies on other ion channels (Lenglet et al., 2017). Plant GLRs are certainly not acting as neurotransmitter receptors. A similar conclusion can be made for GABA receptors. GABA is well-known to participate in stress responses (Shelp et al., 1999), and has recently been shown modulate stomatal opening (Xu et al., 2021). Plant GABA receptors have little sequence homology with their animal counterparts (Ramesh et al., 2017). In short GABA and its receptor are completely unrelated to “neural” activities. Ion channels and the control of membrane potential are inherent to all organisms, all cell types and organs, and they have a very early evolutionary origin (Miller, 2009; Varoqueaux and Fasshauer, 2017; Elliott et al., 2020). It can therefore be expected that they can be found in plants as well as in animals or even protozoa, of which the latter clearly have no nervous system. Likewise, it would be absurd to call the immune system “neuronal” due to the widespread presence of GABA receptors in immune cells (Barragan et al., 2015) or to infer neuronal functions of blood platelets from their expression of glutamate receptors (Kalev-Zylinska et al., 2020).

It has also been recently suggested that plasmodesmata (see Fig. 2) are the plant equivalents of gap junctions and therefore constitute electrical synapses (Mediano et al., 2021). Comparisons between gap junctions and plasmodesmata have been made on numerous occasions over the last 50 years (e.g. Gunning and Robards, 1976; Epel, 1994; Lee, 2015; Peters et al., 2021), but the explicit claim that plasmodesmata are equivalent to electrical synapses (gap junctions) of animal cells is new. Gap junctions do indeed contribute to electrical conductivity, between cells, including multiple cell types in non-neuronal tissues (Szczupak, 2016). This abundance makes them unsuitable as a defining feature of nervous systems, similar to the mere existence of propagating electrical signals. Nevertheless, we can ask what can we say about the propagation of electropotential waves through plant plasmodesmata? The literature on this does not give an entirely clear answer. The first positive indication that plasmodesmata were responsible for electrical conductance between neighboring cells was provided by Spanswick and Costerton (1967) who injected current into a single cell of the alga Nitella and followed its propagation into other cells of the filament. However, the conductivity through the plasmodesmata of higher plant cells is about 100-fold lower than for filamentous algae (see van Bel and Ehlers, 2005 for literature). As stated by Spanswick (1972) “*Although plasmodesmata permit the passage of current, it is estimated that they have a resistance about 60 times higher than would be the case if they were completely open channels*“, this means that they represent only a small fraction of the total conductivity between neighboring cells. On the other hand, Overall and Gunning (1982) working on Azolla root tip cells concluded that intercellular electrical conductance via plasmodesmata was linearly correlated with the incidence of plasmodesmata in the division walls, and pointed out that these declined in number during root growth.

The next question is whether plasmodesmata are present in sufficient number in the longitudinal walls of root cortex cells and whether they may represent efficient channels for electropotential wave conductivity? In their 2018 review Canales et al. give the impression (see their cartoon, Fig. 4) that propagation of electropotential waves from the epidermal cells across the root cortex to sieve elements does indeed proceed via plasmodesmata. However, in their paper on plasmodesmata distribution in roots, Juniper and Barlow (1969) state “*There are many more plasmodesmata traversing transverse walls than across longitudinal walls in all the regions studied*”. This might be expected considering that plasmodesmata are formed by incomplete cell division in

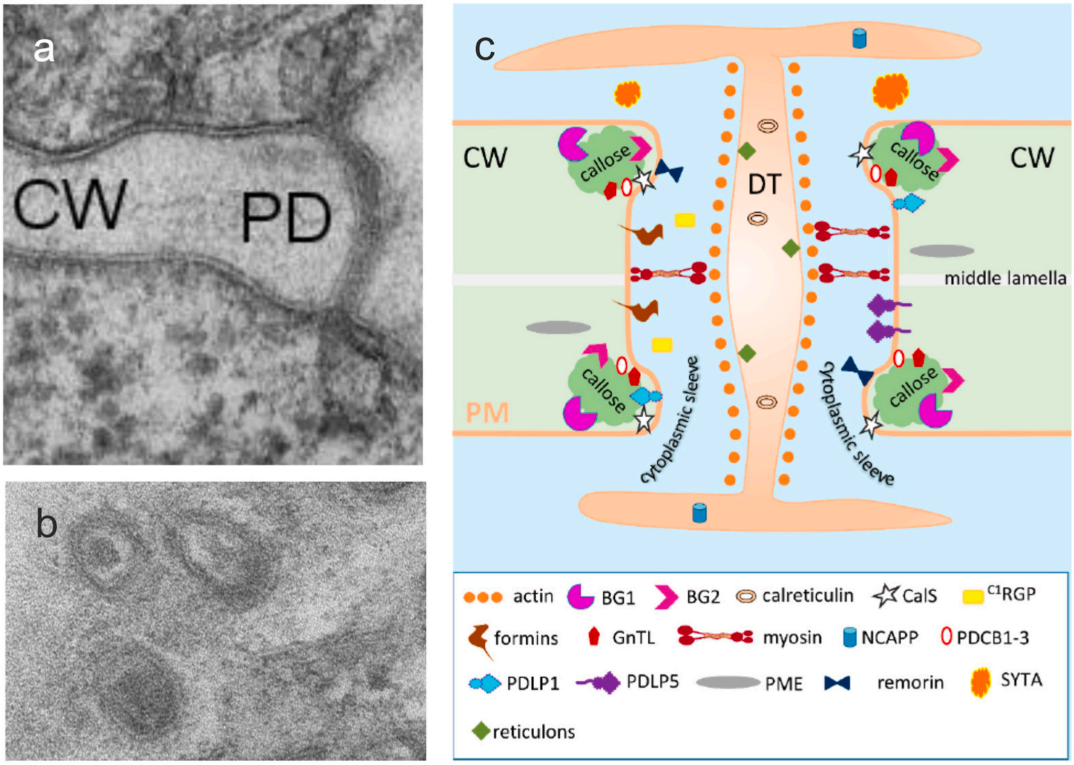

Fig. 2. Plasmodesmata: Plant Synapses? A plasmodesmos in longitudinal section (a). The continuity of the endoplasmic reticulum from one cell to the other, through the pore of the plasmodesmos is visible. The membrane of the ER therefore creates a cylinder inside the plasmodesmatal pore. In cross-section (b), one sees the typical circle-in-a-circle image. (EM images from a high-pressure frozen sample (a) of cells in an Arabidopsis embryo, of chemically fixed maize leaf cells (b). Courtesy of Dr. Stefan Hillmer). c. Cartoon portrayal of the main components in a typical plasmodesma. Intracellular trafficking can occur through the cytoplasmic sleeve that lies between the central cylinder of the desmotubule (DT) and the plasma membrane of the plasmodesmatal pore. The width of the cytoplasmic sleeve is regulated by cytoskeleton elements (actin, myosin), whereas reticulons in the DT membrane appear to control the breadth of lumen of the DT. Closure of the plasmodesma is achieved through callose deposition at the neck of the cylinder. (From Dorokhorov et al., 2019).

cross walls. On the other hand, as pointed out by Ehlers and Kollmann (2001) “*secondary plasmodesmata can be expected to be formed in all those longitudinal cell walls which undergo intensive extension growth, in order to compensate for the progressive dilution of preexisting primary plasmodesmata*”. There is simply insufficient data to make a definitive statement on the incidence of plasmodesmata in longitudinal walls. In conclusion, there is little evidence to support the notion that electropotential wave tranmission from the root epidermis to the phloem occurs by coupled plasmodesmata conductivities along the transit route. In fact, Overall and Gunning (1982) recorded that there is a loss of electrical current during each plasmodesmata transit step, which is in sharp contrast to the loss-free, regenerative conduction of action potentials in nerve cells (see below). So we must concur with van Bel and Ehlers (2005) who wrote “*Given the loss of electrical current during each plasmodesmata passage, one must conclude that an electrotonic propagation* (through plasmodesmata) *should be rapidly extinguished*“. In any case, based on

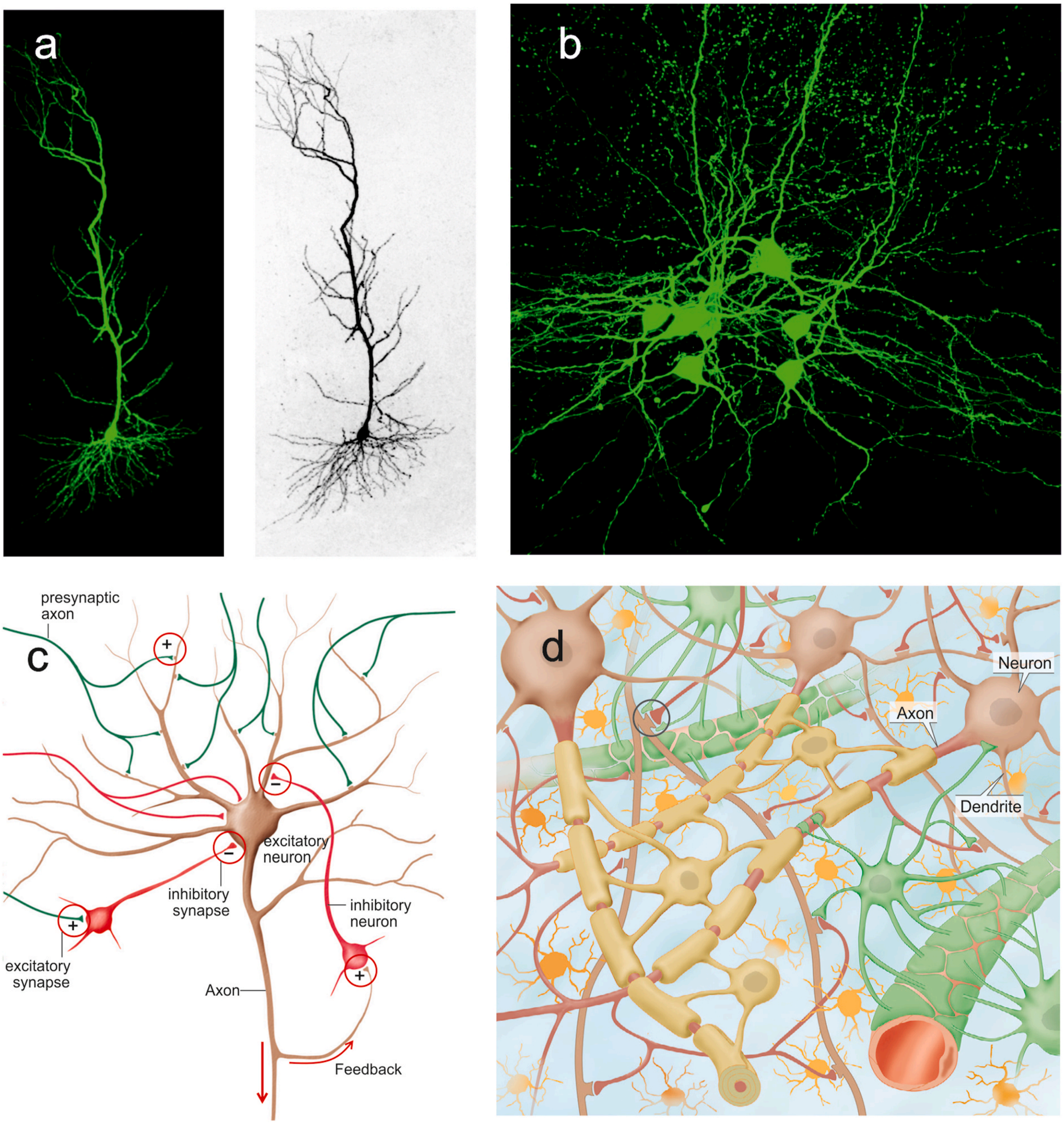

Fig. 3. Neurons and Networks. A single pyramidal cell in the mouse hippocampus (a) and a small cluster of neurons in the mouse entorhinal cortex (b). Note the complex structure of the dendritic tree in the cell in (a), which is targeted by $>$ 20.000 afferent synapses. The single output fiber (axon) is not discernible at this magnification. The cluster of neurons on (b) gives an impression of the dense packing of processes in typical neuronal networks. (Fluorescence stainings courtesy of Dr. Alexei Egorov). Schematic representations in (c) and (d) show basic properties of neuronal networks. In (c) we highlight excitatory (+) and inhibitory (−) synaptic connections in a typical network. The inhibitory neuron on the right (red) is part of a feedback loop: it is excited by the excitatory neuron and projects back onto the same cell to inhibit it. Such feedback loops are a typical structural element of neuronal circuits. The illustration in (d) highlights axonal connections between neurons and includes glia cells, e.g. the isolating myelin sheets around axons formed by oligodendrocytes (beige), astrocytes (green) which are involved in multiple homeostatic functions and immune cells (microglia, dark yellow). In a real network, the extracellular space would be densely filled with similar structures. (Graphical illustrations in c and d from Rüdiger Gay).

the available evidence, any comparison of the electrophysiological processes at plant plasmodesmata with the highly specialized, fast, rectifying and tightly regulated signal transfer along animal nerves and across animal synapses is extremely far-fetched, if not absurd.

3. Is the phloem a giant neuronal network?

The second hypothesis to be analyzed in this paper is that plants possess networks which enable rapid signaling throughout the whole organism, supporting integration of information and cognition (Mediano et al., 2021; Baluska and Manusco, 2021). Similar claims for brain-like organs underlying plant intelligence, all based on different forms of propagating electrical activity, have been made before (Baluska et al., 2004, 2009).

3.1. Again, we begin by asking what are the salient features of neurons and nervous systems in animals?

While the term νεῦρον ("neuron", sinew, cord, nerve) has been used since ancient times, its modern definition as nerve cell was coined by the German anatomist Heinrich Wilhelm Waldeyer (1891). Like the word synapse, the term was rooted in the "neuron doctrine" and was rapidly adopted by the protagonists of the early era of cellular neuroscience (Mehta et al., 2020). Neurons are characterized by their strong polarity, electrical excitability and specific connectivity with other cells (Fig. 3). With these properties, they form complex networks which are able to integrate multiple signals and to produce coordinated responses in multi-cellular organisms. They do so by highly targeted interactions with sensory cells, effector cells (muscles or endocrine cells) or amongst themselves. Communication between neurons is mostly mediated by axons (from Greek ἄξων for "axis", formerly also called "neurite") which propagate action potentials at velocities between $\sim$1 and $\sim$100 m/s. An important feature of axonal signal propagation is its regenerative nature, i.e. the action potential is renewed at every stage of the axon, enabling long-distance communication without attenuation of the signal. In peripheral tissues, bundles of axons form macroscopic nerves which are, hence, a hallmark of organisms with nervous systems. Nervous systems exist in different degrees of complexity, with marked differences between different organisms and brain regions. The idea that cognitive and behavioral functions of animals are tightly linked to, or caused by, the underlying network structure is as old as the neuron doctrine (Ramón y Cajal, 1906) and has been elaborated to specific predictions of structure-function relationships long before high-resolution-observations of neuronal network activity were possible (Hebb, 1949).

Modern studies of neuronal networks have revealed several structural and functional correlates of complex behavior and cognition. These include dense convergent and divergent synaptic connectivity, recurrent connections, hierarchical sequences of networks, modular organization, highly connected hubs, synchronous (oscillating) activity, different functional states, neuronal diversity, synaptic plasticity and many more (Feinberg and Mallatt, 2016; Bassett and Sporns, 2017). While we are far from a complete understanding of nervous systems it is clear that their complex cellular- and network-level properties enable the wide behavioral repertoire of animals. Nervous systems allow for coordinated reactions to external cues and for targeted, adaptive behavior, that may have been a decisive evolutionary advantage for animals, leading to the development of specialized cells for sensation (sensory neurons), motor output (motor neurons) and, later, internal connectivity between these cells (interneurons). Neurons probably developed at an early stage of metazoan evolution, about 600 million years ago (Varoqueaux and Fasshauer, 2017; Miller, 2009). The first neurons and networks may have served to integrate sensory inputs and to coordinate movements, both locomotion as well as internal motility of the digestive system (Jékely et al., 2015; Furness and Stebbing, 2017). Central nervous systems probably developed from the fusion of distributed neuronal networks in bilaterians (Arendt et al., 2016; Miller, 2009). All in all, the evolution of nervous systems seems to have been driven by the advantages of sensory-motor integration, behavioral flexibility and speed, consistent with their evolutionary loss in behaviorally restricted animals like poriferans and placozoans, and their absence in plants (Varoqueaux and Fasshauer, 2017).

Do plants have any organ similar to nervous systems, and could this be the phloem, as recently suggested (Baluska and Mancuso, 2021; Mediano et al., 2021)? Basically the phloem consists of longitudinally threads of connecting elongated sieve elements with adjacent companion cells (usually 3–5 per sieve element; van Bel, 2003) surrounded by phloem parenchyma (Fig. 4). Whereas the companion cells are densely packed with organelles and cytoplasm, the sieve elements have a so-called mictoplasm consisting of cytoplasm diluted with phloem sap and a few organelles (mainly endoplasmic reticulum) (van Bel, 2003). Thus, through plasma membrane continuity via the sieve pores, which are essentially enlarged plasmodesmata, the phloem can be considered to be a low-resistance, long range conduit for electropotential wave propagation (van Bel and Ehlers., 2005). Surrounding, or immediately adjacent to the sieve element/companion cell are phloem parenchyma cells. Although these cells are connected with the sieve element/companion cell via plasmodesmata they are not connected symplasmically (Hafke et al., 2005; van Bel et al., 2014). This does not however imply a full electrical isolation, since a small portion of the electrical current does leak out of the sieve element/companion cell into the phloem parenchyma via plasmodesmata (van Bel and van Rijen, 1994; Rhodes et al., 1996).

The phloem has been described by some as a huge interconnected, sponge-like neural network (Calvo et al., 2017), but this is perhaps an over-exaggerated interpretation. especially regarding the term 'neural' (remember that sponges have no neurons, and true neuronal networks are specifically connected and nothing less than sponge-like). Lateral anastomoses (see Fig. 4 c) are absent from young internodes, but increase in number during development (Aloni and Barnett, 1996). What is important is their functional status: under normal conditions they appear to play a negligible role in assimilate transport (Aloni and Peterson, 1990), a situation that changes dramatically upon wounding. Aloni and Barnett (1996) therefore consider the sometimes dense network of phloem anastomoses in mature tissue to represent "a mechanism of adaptation to possible damage in mature internodes". In the absence of electrophysiological data it is therefore impossible to speculate about possible electrical signal propagation along phloem anastomoses.

Measurement of membrane potentials in sieve elements is usually performed by insertion of a microelectrode (van Bel et al., 2014) or by less-invasive means using either severed aphid stylets (Fromm and Bauer, 1994) or intact aphids (Salvador-Recatala et al., 2014). In intact plants the resting membrane potential of sieve elements varies between −170 mV and −117 mV (Hafke et al., 2005). External stimuli are usually translated into an influx of Ca^{2+} into the cytoplasm. This may be achieved by the opening of Ca^{2+} channels in the plasma membrane (Hafke and van Bel, 2013) or from endomembrane sources (e.g. from the endoplasmic reticulum, see Fig. 4 d). This in turn leads to an opening of Cl^{-} and K^{+} channels. and a consequential change in plasma membrane potential. Three major types of propagating electropotential waves exist: action potentials, variation or slow-wave potentials or system potentials (Hafke and van Bel, 2013; Farmer et al., 2020). In contrast to action potentials and variation potentials, the system potential-hyperpolarization is due to an activation of plasma membrane-located H^{+}-ATPases (Zimmermann et al., 2009). Typically, action potentials are generated by touch or other non-damaging stimuli and have transmission velocities of 0.04–0.6 m/s with long refractory periods between successive action potentials (Canales et al., 2018). In the specialized case of the Venus fly trap the refractory periods are much shorter (Scherzer et al., 2019). But these action potentials are restricted to the local organ and therefore cannot contribute to any system-wide neuronal information processing. Variation potentials are triggered in response to severe tissue damage and travel very slowly (around 0.001 m/s) (Stahlberg et al.,

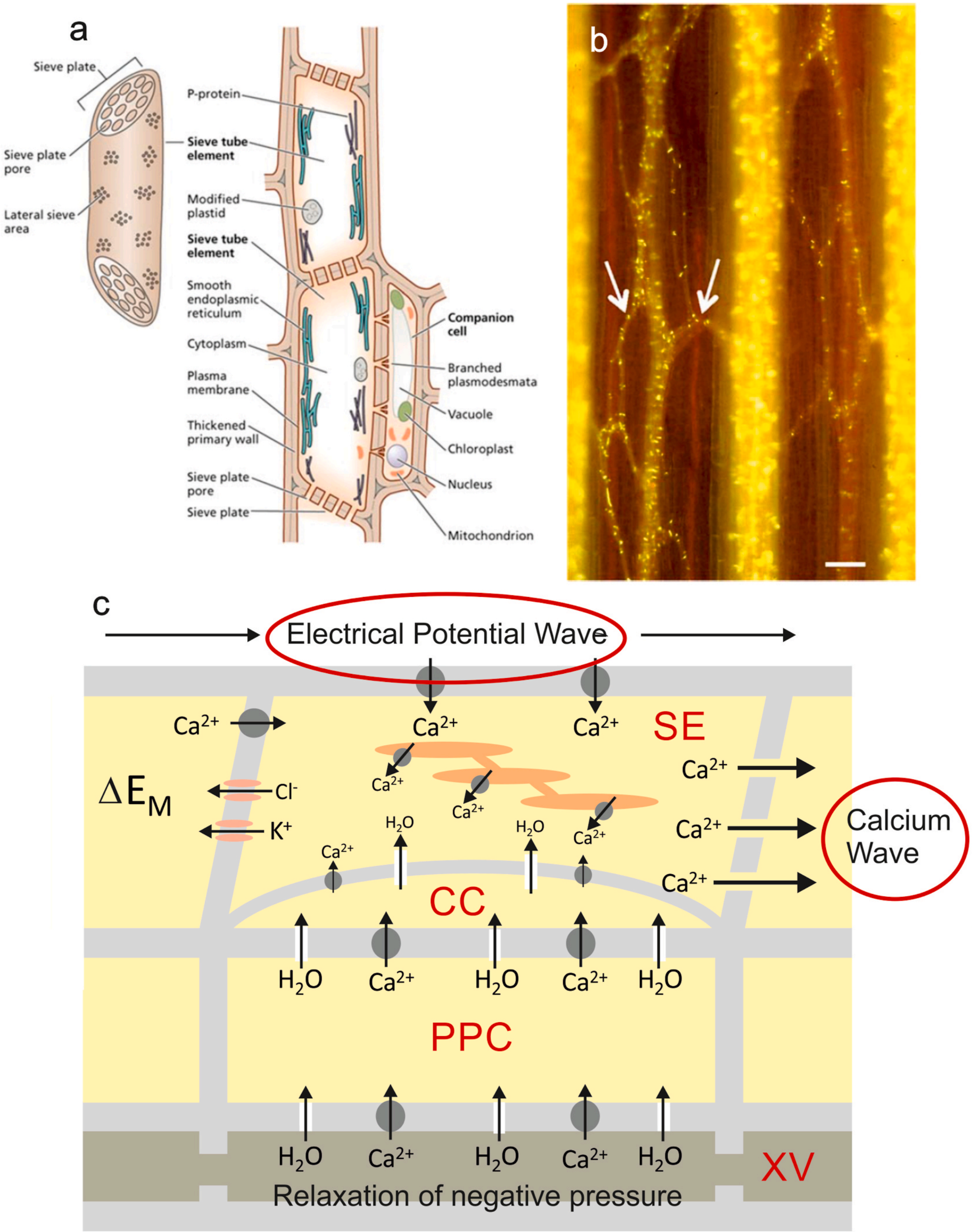

Fig. 4. Phloem Structure and Physiology. The basic cellular components of the phloem (a). Sieve tube elements constitute the major assimilate transporting channels. They are connected to one another vertically at junctions termed sieve plates, which contain large diameter pores. When injured, callose is produced which blocks the pores and assimilate transport stops. During their development, the sieve tube cells lose their nuclei, the tonoplast breaks down and the cytoplasm is mixed with the vacuole sap (mictoplasm). Remaining are modified plastids and sheets of endoplasmic reticulum. Through cell division, companion cells are formed which lie adjacent to the sieve tube elements, and are symplasmically connected with them via plasmodesmata. These may be simple or branched. (b) Lateral connections (anastomoses) exist between major longitudinal sieve tube elements. They increase in number as tissues mature, however, in young stages they appear to be inactive in assimilate transport. Nothing is known about electrical conductivity in anastomoses. The image is a longitudinal section of the phloem in *Dahlia pinnata* which has been removed from the xylem at the cambial zone. The sample was stained with aniline blue. The lateral anastomoses are indicated with arrows. The bright specks are plastids. Scale bar = 100 μm. (c) Electropotential wave propagation in the phloem and Ca^{2+} - based signaling. Membrane depolarization (creation of action potentials) cause an influx of Ca^{2+} into the mictoplasm through voltage-gated channels at the plasma membrane of both the sieve element (SE) and companion cell (CC). Additional Ca^{2+} comes from internal sources, in particular the endoplasmic reticulum. As a consequence of disturbances in water potential, water moves into the sieve element. The result is that a wave of Ca^{2+} accompanies the movement of the electropotential wave. Redrawn and modified from Figures published by Hafke and van Bel (2013), van Bel et al. (2014).

2006; Mousavi et al., 2013). System potentials are large, systemically transmitted hyperpolarizations often caused by feeding herbivores or by chemical treatments (Zimmermann et al., 2016). They have a speed of 5–10 cm/min (~0.001–0.002 m/s; Farmer et al., 2020). Slow-wave potentials can travel from young leaves to old leaves and vice versa, but whether this bidirectional signal propagation can occur simultaneously in the same phloem element is unclear. In any case, electrical processes in plants seem to lack the highly specific, recurrent connections and the complex spatiotemporal electrical patterns required for genuine cognitive processes (Hebb, 1949; Feinberg and Mallatt, 2016).

A widely upheld notion is that the principal purpose of the propagation of electropotential waves is to generate a wave of increasing Ca^{2+} in the interior of the sieve elements (van Bel et al., 2014), which then acts as a mediator for the synthesis of the defense hormones jasmonate and ethylene (reviewed by Farmer et al., 2020). In fact, it has been experimentally demonstrated that wound-induced electropotential waves precede cytosolic Ca^{2+} maxima (Nguyen et al., 2018). This latter paper is additionally of particular significance, because it questions the prevailing view that electropotential wave transmission is restricted to the sieve elements. Employing a novel genetical approach these authors have established that both xylem parenchyma as well as sieve elements are required for wound-induced electrical signaling in leaves.

In summary, electrical signals and their propagation in plants are so different from the specialized signal processing in neuronal networks that any comparison is difficult if not worthless to persue. The idea that the continuum of symplasmic connections in the phloem makes the phloem an ideal substitute for a nervous system reminds one of reticularist theories of the nineteenth century.

4. Conclusion(s)

Synapses, neurons and neuronal networks are highly specialized structures supporting conduction, integration and processing of electrical signals. Their combined properties enable rapid and flexible responses to external cues, adapted sensory-motor behavior, coordination of multi-cellular internal activity patterns and, in highly complex networks with specific properties, cognition. Nervous systems evolved and persisted in three highly motile, actively behaving clades of metazoan animals (Ctenophora, Cnidaria, Bilateralia). We have examined whether functionally equivalent structures exist in plants, as repeatedly suggested by proponents of Plant Neurobiology. Despite metaphorical uses of the word "synapse" for diverse plant-specific structures, including plasmodesmata, there is no evidence whatsoever that these "synapse-like domains" exert any of the functions of neuronal synapses: fast electrical or chemical signal transmission, specificity and diversity of postsynaptic effects, rectification and plasticity. Despite the presence of glutamate and GABA in plants there is also no data to show that they act as neurotransmitters. One can only conclude that plant synapses are a product of the over-fertile imagination of plant neurobiologists.

The same conclusion can be applied to the notion that the phloem represents a "simple neuronal network". Even a cursory look at Figs. 3 and 4 reveals that neurons and phloem are structurally completely different, and hence are unable to serve similar behavioral-cognitive functions. So too are the physiological bases for the generation and conduction of action potentials and other electrical signals in plants. While there is electrical transmission in the phloem of plants, this is related to Ca^{2+} signaling associated with various hormonal responses to wounding. It is in no way comparable to animal nervous systems which are clearly specialized for coordinating sensory-motor behavior and, in some phyla, cognition. Disregarding these differences harms the important process of elucidating the physiology of plants by solid, fact-based science. It also means ignoring the distinct evolutionary history and ecological adaptation of plants and animals. Hence, it is misleading to both young scientists and the general public. Plants are organisms in their own right and should not be turned into animal- or human-like beings by far-fetched metaphors from cognitive neuroscience.

Since the phloem cannot function as the equivalent of a neuronal network, and the latter is required to develop cognitive abiities, suggestions that the level of consciousness in different plants is determined by the quantity of phloem in their vascular systems (Mediano et al., 2021) lack supporting evidence and consequently border on the absurd. One should not forget that even in woody species, living phloem cells rarely function for more than a year and are constantly being shed as "bark". Humans do not regenerate their nervous system or brains every year! Moreover, if phloem is a prerequisite for the consciousness in plants, nonvascular plants like liverworts and mosses, and perhaps some primitive vascular plants as well, would have to be unconscious, even though they actively sense and respond to their environments as higher plants do. For the same reasons, we do not localize cognition in the mammalian vascular system, although it is even more complex and branched than plant phloem and expresses a plethora of local and system-wide signaling pathways.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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