

Neuronal activity creates a reciprocal cationic flux in the extracellular space in the brain: a hypothesis

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Abstract

The fluid in the extracellular space around the neurons and glial cells is enclosed within the cells is enclosed within the brain, kept separate from the circulation and the rest of the body and the rest of the body-fluid. This brain interstitial fluid forms a distinct compartment; a sponge-distinct compartment; a sponge-like “inverse cell” that surrounds all the cells. During neuronal the cells. During neuronal resting and action potentials, sodium and potassium ions shuttle potassium ions shuttle between this “Reciprocal Domain” and the neurons within the brain. This neurons within the brain. This localised flux of ions is the counterpart to all the neuronal counterpart to all the neuronal electrochemical activity (having the same intensity and duration, same intensity and duration, at the same sites in the brain), so a complementary version of all complementary version of all that potential information is integrated into this extracellular space into this extracellular space within the brain. A mechanism is proposed whereby this flux of proposed whereby this flux of cations in the Reciprocal Domain may also indirectly influence also indirectly influence neuronal activity in the brain, creating immensely complex feedback. immensely complex feedback. This Reciprocal Domain is unified throughout the brain, and throughout the brain, and exists continuously throughout life. This model identifies which model identifies which species have such enveloped extracellular spaces, and how many times

spaces, and how many times similar systems evolved. This account of the brain could have the brain could have clinical implications; the Reciprocal Domain could be vulnerable to could be vulnerable to disruption by chemical insult, traumatic injury or pathology. These are or pathology. These are key characteristics of our core selves, which encourages the idea that encourages the idea that this Reciprocal Domain is crucial for the brain. This hypothesis is brain. This hypothesis is explored and developed.

Introduction

In this manuscript, I consider the biology of the brain, looking at how the electrochemical activity of the neurons affects the rest of it, and how that activity might be affected in return. Instead of regarding the brain as just a network of interconnected neurons, which processes incoming information to determine outward signals; I put forward a model of the brain as comprising of two distinct, but interacting, biological parts: the network of neurons, and a Reciprocal Domain.

Background

The neurons are the cells in the brain that attract the most interest. For example, the distinguished thinker Francis Crick summarized his *Astonishing Hypothesis*, in a pastiche of Lewis Carroll, as, “You’re nothing but a pack of nothing but a pack of neurons” {Crick, 1994}. The human brain contains around 10^{11} neurons; however, there are many more non-neuronal cells, which attract far less attention. Neurons tend to be the focus for contemporary brain research because they are “excitable” cells. That is, their surface changes rapidly in response to stimulation; an impulse (an action potential, or spike), as Ramon y Cajal first suggested, passes quickly from one end of the cell to the other, where an action potential may be triggered in the next neuron. Thus, neurons appear to be the “active” parts of the brain. This has rather been taken to imply that the rest of the brain is passive, or unimportant. However, this idea is misleading. An analogy: one would not try to explain an internal combustion engine only in terms of its moving parts. The valves, pistons and

parts. The valves, pistons and crankshaft move; but their activity can only be understood within only be understood within the context of the whole engine; therefore, this study will try to this study will try to consider the neurons, and their activity, within the wider biology of the brain. within the wider biology of the brain.

Neurons are not electronic. Unlike solid-state electronic components, to which they are to which they are sometimes misleadingly compared, neuronal activity is not based upon the is not based upon the movement of electrons from one end to the other. The processes of The processes of neuronal excitation were discovered in the middle of the 20th Century: Briefly, the 20th Century: Briefly, the Hodgkin-Huxley model describes the excitation of neurons based excitation of neurons based upon the movement of ions across the plasma membrane into and plasma membrane into and out of the cell {Hodgkin & Huxley, 1952}. Neurons use metabolic Neurons use metabolic energy to pump ions across the plasma membrane, creating a resting creating a resting potential at their surface {Figure 1}. Sodium ions (Na^+) are pumped out of the (Na^+) are pumped out of the cell cytoplasm, in exchange, potassium ions (K^+) are pumped into (K^+) are pumped into the cytoplasm from the extracellular fluid surrounding the neuron. Both surrounding the neuron. Both species of ions are transported across the plasma membrane the plasma membrane against their concentration gradients, by a protein called the Na^+/K^+ - protein called the Na^+/K^+ -ATPase (Figure 1). The concentrations of these cations are different these cations are different inside the cell, compared with the outside, which polarizes the outside, which polarizes the membrane. During the resting potential, there is more than 10 times there is more than 10 times the concentration of sodium ions immediately outside the cell immediately outside the cell compared with inside, and around 20 times more potassium ions more potassium ions inside the cell than outside {Hodgkin, 1958}. This process requires process requires metabolic energy. The brain uses a disproportionate amount of metabolic amount of metabolic energy (approximately 20% of total energy consumed by roughly 2% of

by roughly 2% of adult body weight) because of the need for the neurons to establish and maintain resting potentials.

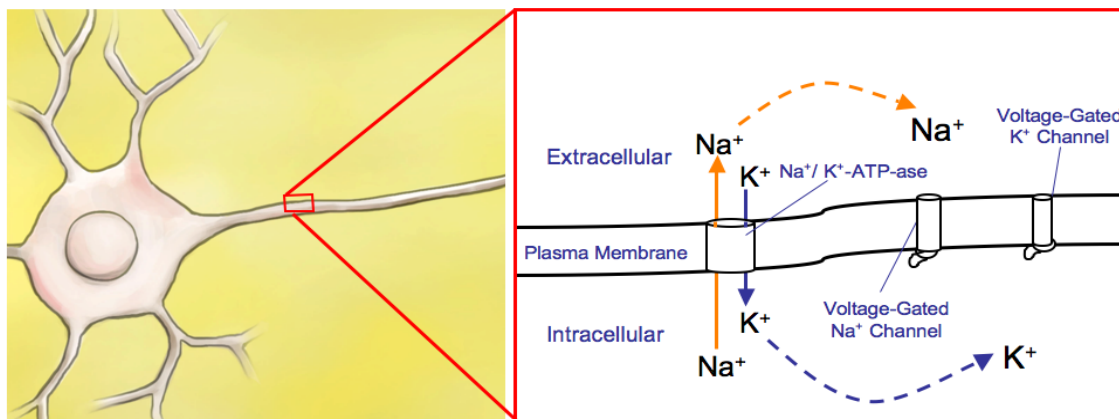


Figure 1: Pumping cations across the neuronal plasma membrane establishes the resting potential. A cross-section of the plasma membrane of a neuron showing part of the inside of the cell (intracellular) and outside the cell (extracellular) (not to scale). Sodium ions (Na^+) are pumped out of the cell, whilst potassium ions (K^+) are pumped into the neuron, by a protein called the Na^+/K^+ -ATP-ase. This polarises the membrane. Note that the voltage-gated ion channels in the plasma membrane are closed.

An action potential, or *spike* – the rapid depolarization of a region of the neuronal plasma membrane neuronal plasma membrane – occurs when sodium ions flood back across the plasma membrane into plasma membrane into the neuron, and then potassium ions pass back out of the cell into the the cell into the surrounding micro-environment {Figure 2}. These movements are passive, in that they are passive, in that they do not require metabolic energy, as the ions travel down their concentration-

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travel down their concentration-gradients and equilibrate across the membrane, through specific ion membrane, through specific ion channels. The ion channels are reversibly gated trans-membrane gated trans-membrane proteins: they change conformation in response to local changes in the voltage local changes in the voltage across the membrane. This opens an aqueous pore across the pore across the membrane that allows specific ions to flow across it. The flux of ions across the flux of ions across the plasma membrane, both into and out of the cell, changes the voltage across it, changes the voltage across it, which triggers the opening of nearby voltage-gated ion channels. Thus voltage-gated ion channels. Thus the depolarization of the plasma membrane at one point triggers the at one point triggers the neighbouring region to depolarize, and so on. This trigger only proceeds in This trigger only proceeds in one direction along the membrane, as channels are not receptive to are not receptive to triggering for a few milliseconds after having been open. This type of activation open. This type of activation moves along the neuron as a metachronal – rather than synchronous – rather than synchronous – wave; the impulse travels along the surface of the neuron from the the neuron from the dendrites along the axon. An analogy with the propagation of an action potential propagation of an action potential along the neuronal plasma membrane is the “Mexican wave” in the “Mexican wave” in sports stadiums, where the wave travels around the crowd as individuals crowd as individuals quickly stand up and sit back in their own seats, triggered by the same action of triggered by the same action of their neighbour just before them. The wave rushes around the rushes around the stadium; but the spectators do not. Similarly, the wave of depolarization runs along of depolarization runs along the membrane of the neuron, as ions flow into and out of the cell, rather and out of the cell, rather than charged particles flowing along the interior of the cell.

interior of the cell.

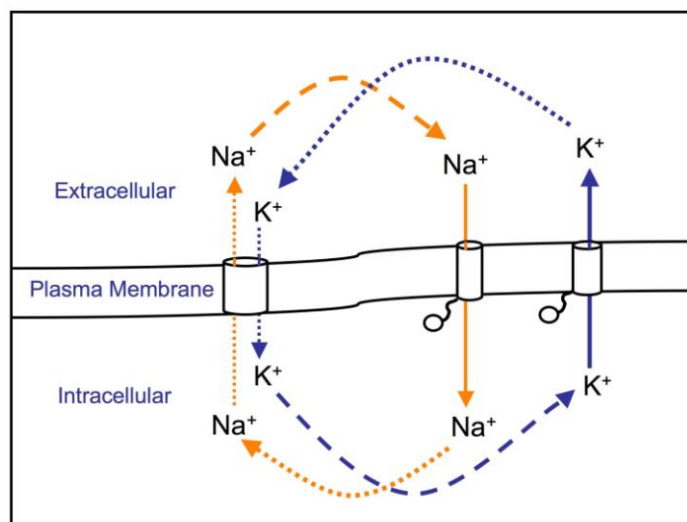


Figure 2: The action potential occurs when the gated ion channels briefly open. This depolarises the membrane as sodium ions (Na^+) and then potassium ions (K^+) equilibrate across the plasma membrane. This causes a spike, or change, in the potential difference across the plasma membrane, which triggers the opening of neighbouring voltage-gated channels.

The excitation of one neuron can trigger the excitation of a neighbouring neuron. This stimulation may be electrical, via electrical contact across gap junctions, or chemical transmission across a synapse. The fusing of intracellular vesicles with the plasma membrane at the synapse releases neurotransmitter into the synaptic cleft is triggered when the pattern of action potentials received at the synapse is above a threshold in an “all-or-none” process. Synaptic nerve transmission is regulated through the frequency or pattern of action potentials, rather than their amplitude.

In summary, the activity of the neurons of the brain is not like that of contemporary electronic contemporary electronic components, or non-excitable cells. Neurons use metabolic energy to pump sodium and potassium ions across the plasma membrane, polarizing it, and membrane, polarizing it, and creating a resting potential. Upon stimulation, the ions pass through

stimulation, the ions pass through specific gated ion channels in the plasma membrane, down their plasma membrane, down their electrochemical gradients, creating an action potential. This changes potential. This changes the voltage across the plasma membrane of the neuron, which in turn affects neuron, which in turn affects the voltage across the neighbouring region of the neuronal membrane, the neuronal membrane, which opens further voltage-gated ion channels, leading to further leading to further depolarization, and so forth. Thus, a metachronal wave of depolarization, rapidly of depolarization, rapidly followed by repolarisation, travels along the membrane of the neuron from membrane of the neuron from the dendrites, across the cell body, and along the axon. Physical the axon. Physical particles, such as electrons, do not “flow” through the cell to create a current; it is cell to create a current; it is not a tube or wire. As the wave of excitation travels along the neuron, the excitation travels along the neuron, the movement of ions across the plasma membrane is at right membrane is at right angles (orthogonal) to the direction of the nerve impulse along the membrane of impulse along the membrane of the neuron. The amplitude of the impulse travelling along the neuron travelling along the neuron is determined by the local gradients of ions across the membrane. across the membrane. Providing that there is a sufficiently large electrochemical gradient, then the electrochemical gradient, then the wave of depolarization propagates along the neuron, in an “all-or-the neuron, in an “all-or-none” system. The pattern and rate at which impulses reach the synapse, impulses reach the synapse, rather than their amplitude, determine whether neurotransmitter is neurotransmitter is released at the synapse, in another “all-or-none” system. system.

Neuronal Activity Causes a Complementary Change in the Brain

The preceding brief account of the Hodgkin-Huxley model of neuronal excitation introduces the excitation introduces the subject. The cross-sectional diagrams in Figures 1 & 2 show the movement 1 & 2 show the movement of cations into and out of the neuron; but these illustrations can also be illustrations can also be looked at in another way: they might be seen as showing the corresponding showing the corresponding movement of ions into and out of the micro-environment surrounding the

environment surrounding the neuron. The similarities between the fluxes on both sides of the plasma membrane both sides of the plasma membrane become apparent if the illustration is rotated through 90° – and rotated through 90° – and the labelling simplified so that the cations are unspecified – then we may see that the two sides of the membrane in a cross-sectional illustration cross-sectional illustration appear to have similar fluxes of ions {Figure 3}. Upon examination, we can see that the ionic fluxes on the two sides of the plasma membrane are the plasma membrane are not the same; they are complementary. That is, as an ion leaves one side an ion leaves one side of the membrane, it crosses the plasma membrane, and appears on the other appears on the other side. There is one less of those ions on one side, and one more on the other. one more on the other. Thus, the two sides of the membrane may be considered as part and counter-considered as part and counter-part – in the sense that fossils in sedimentary rock may cleave into sedimentary rock may cleave into two complementary forms: one side convex, the other concave. the other concave. They both have the same pattern, or information, at the same site; however, the same site; however, the part and counterpart are complementary impressions of each other. of each other.

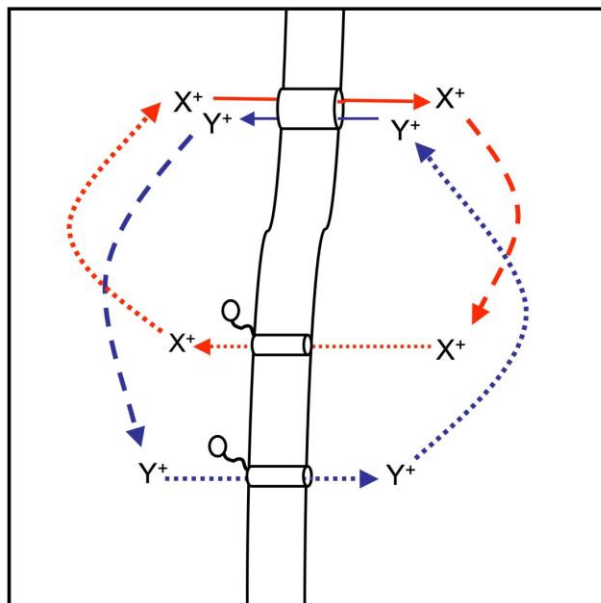


Figure 3: The electrochemical fluxes on the two sides of the plasma membrane are complementary. When the cross-sectional diagram is rotated, and the labelling simplified, it is clear that the movement of the

electrically-charged particles (ions) across the plasma membrane is at right-angles (orthogonal) to the direction of movement of the wave of depolarisation, along the plasma membrane.

The Structure of the Brain Creates a Realm that is Complementary to the Neurons

The flux of ions between the neurons and the surrounding micro-environment might appear to be a fleeting effect that will be quickly washed away by the circulation. After all, the micro-environment around the cells in most other organs are constantly perfused by fluid from the blood plasma, bringing nutrients and removing waste. So the circulation might be expected to constantly refresh the micro-environment around the neurons; however, the structure of the brain prevents this: The meninges are three membranes – the pia, arachnoid and dura – that surround the brain. The choroid plexus also forms part of this continuous envelope that surrounds and encloses the neuronal tissue of the brain, keeping it separate from the circulation. Ependymal cells form pseudo-epithelial cell layers within the brain, which line the ventricles. They partially enclose the neurons from the cerebrospinal fluid, whilst gently washing interstitial fluid over the neurons and glia by the rhythmic beating of their cilia.

The human brain is served by approximately 400 metres of blood vessels. In the late 19th and early the late 19th and early 20th Century, Ehrlich and Goldman found that stains perfused through the perfused through the blood vessels of the brain do not permeate the tissue and stain the surrounding and stain the surrounding cells. Unlike in most other organs, fluid and small molecules cannot flow small molecules cannot flow freely from the lumen of the cerebral blood vessels into the surrounding vessels into the surrounding tissues of the brain. This separation of the circulation from the brain circulation from the brain tissue is due to the blood-brain barrier (BBB). It has subsequently been

It has subsequently been discovered that, in mammals, the endothelial cells that line the blood vessels that line the blood vessels bind each other via tight junctions that prevent even small hydrophilic prevent even small hydrophilic molecules from passing between these cells. This effectively seals the This effectively seals the vessels, stopping the nutrients and ions of the plasma simply washing out plasma simply washing out from the lumen of the vessel, over the surrounding neurons. The nutrients surrounding neurons. The nutrients and ions have to be transported across the membranes of the the membranes of the endothelial cells, either into the brain interstitial fluid, or directly to the neurons fluid, or directly to the neurons via astrocytes.

The meninges, choroid plexus and BBB combine to form an envelope, or barrier, around the brain, barrier, around the brain, which isolates it from the rest of the body. The brain interstitial fluid (BIF) that brain interstitial fluid (BIF) that surrounds the cells of the brain, including the neurons, is distinct from including the neurons, is distinct from the plasma of the circulation. It has a much lower protein has a much lower protein concentration, and few circulating cells. Nevertheless, it does contain some Nevertheless, it does contain some nutrients, neuromodulators and inorganic ions. It flows slowly ions. It flows slowly around the brain, without mixing with the blood. The BIF micro-environments BIF micro-environments around the neurons of the higher brain form a continuous entity: a unified continuous entity: a unified “Reciprocal Domain” within the brain. This Reciprocal Domain might be Reciprocal Domain might be considered as the *Negative Space*, which surrounds the neurons, surrounds the neurons, sealed within the brain.

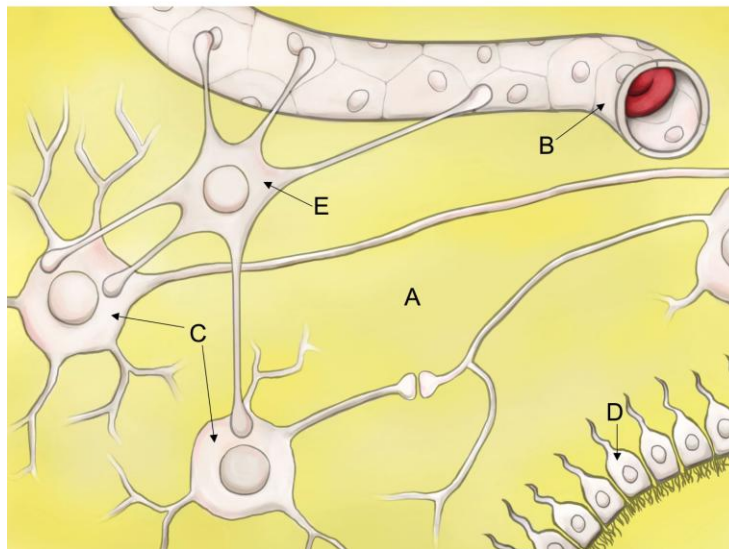


Figure 4: Illustration of the Reciprocal Domain around the cells within the brain (not to scale). A = the golden brain interstitial fluid (BIF), which forms the Reciprocal Domain when enveloped within the brain. B = capillary blood vessel, part of the blood-brain barrier (BBB), cross-section showing a red blood cell. Note that the endothelial cells that create the capillary form tight junctions with each other; fluid cannot pass from the plasma in the lumen of the vessel to the Reciprocal Domain. C = neurons. D = ependymal cells. E = an astrocyte, a type of glial cell, this one is in contact with neurons and the capillary; it is involved in transporting nutrients from the plasma in the vessel to the neurons.

The separation of the neurons, glial cells and the surrounding BIF from the rest of the body-fluid has been interpreted as a form that has evolved to maintain the neurons in a constant environment, away from fluctuations in the blood-levels of nutrients, ions and hormones. That explanation is the opposite of this new model, in that it emphasizes the homeostasis of the extracellular fluid in the brain; whereas this new idea focuses upon the flux of cations in the micro-environment around the neurons, caused by their activity. The BBB has also been interpreted as a protective feature, preventing the neurons from being exposed to ingested poisons or systemic infections. Such a description of the BBB does not preclude the idea that this structure may also

this structure may also envelop the neurons and their surrounding micro-environments within the environments within the brain, creating this Reciprocal Domain.

Is This Reciprocal Domain Just an Epiphenomenon?

Changes in the Reciprocal Domain considered so far might be just local effects within the brain caused by the activity of neurons. If this is the case, then the electrochemical flux in the Reciprocal Domain is only an epiphenomenon – an accompaniment that does not contribute to the activity of the brain; however, if it is found that changes in this extracellular space within the brain may cause some effects, then it would warrant further exploration. This possibility is considered in the following sections.

The Reciprocal Domain and Perception

Current theories of perception tend to focus upon the pathway from sensory receptor cells, which when excited, trigger excitations in a series of neurons, so that the “signal” – the *information* – is passed along a pathway, which causes neuronal activity at a specific site in the neo-cortex (a “neuronal correlate of the sensation”). However, this kind of explanation seems to leave a large gap at the centre – raising what has been termed *the Hard Question*: “... and then what happens?” {Dennett, 1991}. According to such models, it would seem that there is nothing – or no-one – in the brain to integrate and interpret the neuronal activity that has been initiated in the cortex following stimulation of sensory receptor cells. If the brain is considered as just a pack of neurons, then there appears to be no particular neuron, or set of neurons, that is privileged to be the centre that experiences the sensation.

This new model of the brain points towards an answer to the Hard Question. The receptive surfaces of the body map to the surface of the brain, so that excitation of receptor cells in certain parts of the body triggers excitation along a pathway of neurons, leading to the excitation in a specific region of the neo-cortex (the neuronal correlate of the sensation). This neuronal excitation also causes electrochemical flux in the Reciprocal Domain around those particular neurons. A neuronal correlate of sensation creates an electrochemical change at the same specific site, but in the Reciprocal Domain, a larger entity shaped around all the cells in the brain, which is patterned by all the neuronal electrochemical activity. Thus, the Reciprocal Domain could be the experiential centre within the brain.

Could the Reciprocal Domain Influence Neuronal Activity?

As has been noted, neurons are excitable cells whose activity is triggered by interactions with other excitable cells, including other neurons. They seem to be the active parts of the brain: could their activity be altered by the Reciprocal Domain? To consider this matter, the subsidiary hypothesis is: naturally-occurring changes in the cationic micro-environment surrounding neurons in the brain can influence their activity. To distinguish between two possible types of influence upon neuronal activity: neurons are here designated to have a direct influence upon each other via synapses or gap junctions. These are the classical methods of neuronal stimulation and inhibition. The Reciprocal Domain will be considered to have an indirect influence upon neurons if changes in the extracellular electrochemical flux can alter their activity.

The lack of extracellular matrix (ECM) in the brain brings neurons close together. This proximity means that the micro-environment around neurons overlap with each other. The micro-environment around neurons during resting potentials is different from that during action potentials, and as the micro-environments around neighbouring neurons overlap and mix, so adjacent neurons contribute to the micro-environment surrounding each other. That is, the electrochemical flux in the interstitial fluid immediately surrounding each neuron is the product of the activity of more than one neuron. So the composition of the micro-environment that is calculated or measured *in vitro* for individual cells does not necessarily reflect that found around neurons in the brain. Could such local, temporary changes in the electrochemical composition of the Reciprocal Domain affect neuronal activity?

An action potential can propagate along a neuron providing that the electrochemical gradients across the plasma membrane are sufficient at all points along the cell. This ensures that there is a large enough spike (change in potential difference across the membrane) to trigger the depolarization of the adjacent region of membrane, so that the metachronal wave propagates along the membrane of the neuron. In “all-or-none” systems, such as the propagation of action potentials along a neuron, there is a “tipping point” when a relatively small difference can change the system from one state to the other: the switch between propagation and attenuation. Therefore, in certain situations, relatively small local changes in the electrochemical gradient across the membrane may – in theory – stop the propagation of a neuronal spike.

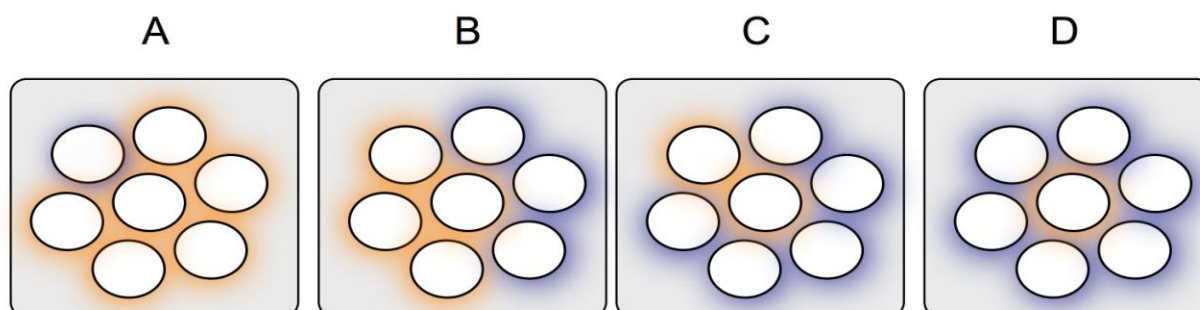


Figure 5: An illustration of how changes in the extracellular Reciprocal Domain (caused by neighbouring neuronal activity) might indirectly influence action potentials. Transverse cross-sections of adjacent neurons. Extracellular regions richer in sodium ions (during the resting potential) are shown in orange. Micro-environment temporarily relatively rich in potassium ions (during the brief action potential) are in lilac. Note that the micro-environments overlap and change each other.

A possible scenario for indirect influence of the Reciprocal Domain upon neurons is illustrated in neurons is illustrated in Figure 5. A cluster of neurons is shown in cross-section, indicating where the section, indicating where the micro-environments around the neuronal processes overlap. The micro-processes overlap. The micro-environments around the neurons are shown in either orange – to indicate the higher sodium, lower potassium micro-environment created during a resting potential; or lilac, to indicate the brief interval when the micro-environment is higher in potassium, but lower in sodium ions, during an action potential. In figure 5, parts B, C and D show increasing proportions of

show increasing proportions of the neurons surrounding the central one with micro-environments higher in potassium during their action potentials. When the central neuron has a cross-section that is surrounded by a higher potassium micro-environment, then an action potential along the central neuron in this illustration might be stopped, because the local potassium and sodium ion-gradients across the plasma membrane at this point may be insufficient for the spike to propagate. This local dip in the trans-membrane electrochemical gradients would be very brief – lasting only milliseconds – but it might be sufficient to stop an action potential propagating along a neuron if they coincide.

This indirect influence of the Reciprocal Domain upon neuronal activity may seem unlikely because action potentials of several neurons will have to occur simultaneously around a particular region of a neuron. However, the brain contains tens of thousands of millions of neurons, producing action potentials sporadically or rhythmically, which greatly increases the chance of this indirect influence. The disruption of an action potential travelling along the surface of a neuron may not appear a significant event; however, pre-synaptic neurotransmitter release is determined by the rate and pattern at which action potentials reach the synapse, in another “all-or-none” process, so the disruption of an action potential could prevent a release of neurotransmitter into the synapse. This could create a wide range of effects in the brain: for example, through this process, changes in the Reciprocal Domain might indirectly influence either stimulatory or inhibitory neuronal activity, so activity might be initiated by inhibiting inhibitory neurons. This suggests a way that the Reciprocal Domain might indirectly influence the activity of specific neurons, and taken together with the

taken together with the topographic mapping of the motor cortex, this may begin to explain how we begin to explain how we move and act.

The indirect influence of the Reciprocal Domain upon the activity of neurons is different from either synaptic or non-synaptic communication between neurons. Those methods of cell-cell communication are based upon the release of a chemical into the extracellular space by a neuron. This compound binds to a receptor protein in the membrane of a neuron, which changes the activity of the neuron. The Reciprocal Domain can influence neuronal activity when the concentration of cations in the extracellular space is changed by the activity of neurons. This can change the electrochemical gradients across the plasma membrane of neighbouring neurons, which can disrupt the propagation of action potentials.

Can we predict with certainty whether an action potential passing along the central neuron in Figure 4 would propagate past the cross-section shown? Even if all the direct influences are known, we can only predict this with certainty if we also know the indirect influence upon this cell. That is, whether those surrounding neurons have resting or action potentials at the particular instant when the action potential passes through the cross-section. The activity of each of those neurons surrounding the original central neuron in the example may be, in turn, indirectly influenced by the activity of the neurons that surround them. And each of them, in turn, may be indirectly influenced by the neurons that surround them, and so on. Thus, the neurons are not just joined together in a complex “network” of direct interactions (via synapses and gap junctions) but are also “integrated” into a unified whole by the indirect influences of the Reciprocal Domain.

Reciprocal Domain.

The Reciprocal Domain may indirectly influence the “all-or-none” processes of neurons, such as the propagation of action potentials, and the release of neurotransmitter. Changes in this indirect influence may flip the activity of a neuron over a tipping point, having a disproportionate effect. Interactions between neurons and the Reciprocal Domain may iteratively feed back upon each other: for example, the Reciprocal Domain may change the activity of a neuron, which can directly influence the activity of other neurons. This change in neuronal activity will also change the electrochemical flux around them, changing those regions of the Reciprocal Domain, which could indirectly affect further neuronal activity, and so forth. Such cycles of feedback can create enormous complexity.

Does this model suggest that the influence of the Reciprocal Domain upon the activity of the neurons the activity of the neurons of the brain means that efferent activity is not completely determined by not completely determined by afferent activity? The propagation of any particular action potential will particular action potential will be directly influenced and triggered by the activity of the neurons in the the activity of the neurons in the network, but will also be indirectly influenced by the electrochemical influenced by the electrochemical flux that is integrated into the Reciprocal Domain, and the recursive Reciprocal Domain, and the recursive feedback loops between the two realms. The propagation of The propagation of any specific action potential cannot be predicted with certainty, unless the activity certainty, unless the activity of all the integrated neurons at that particular instant is known – and particular instant is known – and thereby the indirect influence of the Reciprocal Domain – which is Reciprocal Domain – which is beyond measurement or computation. Perhaps we should say that the should say that the interaction of direct and indirect influences creates such enormous complexity in such enormous complexity in this biological system that the integrated whole is beyond calculation?

whole is beyond calculation? The brain seems to be a deterministic system – but, in practice, it is but, in practice, it is beyond accurate measurement and calculation – limiting our knowledge and limiting our knowledge and ability to predict its activity with certainty.

This Reciprocal Domain of the Brain Has Intriguing Properties

This Reciprocal Domain could be an important part of the brain. It is an entity that is created and shaped by the structure of the brain, and electrochemically patterned by the activity of all the neurons. It is changed at specific sites around “neuronal correlates of sensations”; it may indirectly influence the activity of some neurons, and form part of a complex loop of feedback affecting neuronal activity. This complexity could make the network of neurons in the brain more responsive and flexible than the role of processor of information that has previously been assigned to it. These are some properties that we might reasonably associate with the mind, which raises the question: could the Reciprocal Domain be the core self, or mind?

The characteristic most closely associated with the mind is consciousness; however, this has proved a however, this has proved a slippery concept to grasp, so it has not been a useful criterion for useful criterion for identifying this important aspect of the brain. Perhaps it will be more useful to list Perhaps it will be more useful to list other characteristics that we may expect of the mind, and see expect of the mind, and see whether the Reciprocal Domain has any of these traits? Any candidate traits? Any candidate proposed to be the mind might reasonably be expected to have some special to have some special properties: the entity should be affected by the activity of incoming (afferent) activity of incoming (afferent) neurons all around the higher brain. It should also be able to change the should also be able to change the activity of outgoing (efferent) neurons – so that we can move our so that we can move our bodies. It should form a unified whole so that it can engage with – experience

can engage with – experience – sites of neuronal activity all around the brain, which are associated with different sensations. It should develop in infancy, and endure through life. The candidate should be susceptible to chemical changes, such as intoxication by narcotics, reversible interruption through sleep or general anaesthetics; suffer physical impairment through injury to the brain or disease. Other animate creatures should share a similar feature.

The Reciprocal Domain is patterned by neuronal activity: the flux of cations into and out of it is caused by the activity of all of the neurons, including the random spikes and resting potentials. Specific sites of it are changed, at particular times, when neurons increase activity, such as during neuronal correlations of sensations. This Reciprocal Domain may alter the activity of neurons within the brain, making their activity unpredictable. It forms a unified whole within the brain that is in contact with all the neurons, as it is shaped around them. This Reciprocal Domain develops in infancy, and endures through life. It is a biological entity, so it might be vulnerable to the chemical and physical factors that change the brain and are known to affect the mind, such as drugs, trauma or disease. These are intriguing features for a novel part of the brain; these qualities encourage the hypothesis that the Reciprocal Domain is the mind. This idea shall be developed and explored.

A Model of the Reciprocal Domain of the Brain as the Mind

The extracellular space within the brain forms a distinct aqueous environment around the neurons. The model developing here is that the activity of the neurons in the brain causes a flux of cations in this Reciprocal Domain, so that a

Reciprocal Domain, so that a counterpart to all the neuronal activity is integrated into this space. Integrated into this space. Importantly, both the resting and action potentials contribute to this potentials contribute to this electrochemical flux. This creates an entity that exists continuously – that exists continuously – although it is constantly changing – throughout the life of the individual. the life of the individual. Local changes in neuronal activity, such as “neuronal correlates of “neuronal correlates of sensations” triggered by stimulation of the senses, change the ionic flux in the change the ionic flux in the particular region of the Reciprocal Domain surrounding those neurons. surrounding those neurons. These are hypothesised to be specific events within the mind. within the mind.

In an idealized, or isolated, system of complementary spaces either side of a membrane: if the flux on one side were known, then the flux on the other side could be simply calculated – just as the sequence of the complementary strand of DNA can be easily deduced from the sequence of a single strand. The ionic fluxes on either side of the membrane are complementary versions of the same pattern, effectively the same information, about the electrochemical activity across the plasma membrane of that neuron, at that particular time, at those specific co-ordinates in the brain. One part determines whether neuronal spikes propagate, and neurotransmitter is secreted, in all-or-none processes, whilst the extracellular counterpart may contribute to, and combine with, the flux around the neighbouring neurons. So there are two distinct – but interacting – realms in the brain that complement each other.

The Structure of This Hypothetical Mind

The BIF forms a continuous environment throughout the extracellular space within the higher brain, so within the higher brain, so this Reciprocal Domain is a material object with physical properties. It is

with physical properties. It is topologically extremely complex, as it surrounds, and is surrounded by, surrounds, and is surrounded by, all the neurons, glia and other cells in the higher brain; the boundary the higher brain; the boundary around this compartment is formed by the plasma membranes of all the plasma membranes of all the cells within the brain. This effectively makes a single extracellular a single extracellular compartment – an “inverse cell” or “sponge” – around all the cells, including the all the cells, including the neurons. This realm is separated from the rest of the body fluid. It sits within of the body fluid. It sits within the higher brain as a unified, continuous whole; however, if this entity is whole; however, if this entity is the mind, then it cannot be uniform. It must have spatial structure for it must have spatial structure for it to engage with the architecture – the spatial arrangement – of the spatial arrangement – of the brain.

Topographic Maps in the Brain and the Unified Non-Uniform Mind

The neurological pathways from a number of sensory surfaces of the body – such as the skin, cochlea such as the skin, cochlea and retina; along with some motor centres – project onto the brain cortices project onto the brain cortices in systematic spatial order to form topographic maps of the body. topographic maps of the body. Sensations from the body cause neuronal activity at the surface of the activity at the surface of the cortex in an ordered manner; neighbouring parts of the body map onto parts of the body map onto adjacent areas of the brain. This topographic mapping in the CNS raises mapping in the CNS raises tantalizing questions, and provokes ideas, about the nature of the brain the nature of the brain and the mind, and their interaction: why have topographic maps repeatedly topographic maps repeatedly evolved for the perception of different senses? Why are there similar Why are there similar maps for both sensory and motor systems? These topographic maps indicate topographic maps indicate that the brain is spatially organized, that information about the site of the information about the site of the body where the stimulus originates can be inferred from the position inferred from the position of the activity induced in the cortex. Topographic mapping also seems to Topographic mapping also seems to imply that there is some neo-Kantian entity that “reads off” the entity that “reads off” the site of any change in neuronal activity from the topographic map. This

the topographic map. This suggests that the mind is also extended in space, about the size of the about the size of the brain, and able to detect and distinguish changes in neuronal activity at different neuronal activity at different sites all over the brain.

The new model of the Reciprocal Domain as the mind begins to explain the topographic mapping of the brain, as topographic mapping can tell us about the nature of the mind. The Reciprocal Domain is spread across the extracellular space in the brain, as an “inverse cell” in contact with all the neurons. A stimulation at a particular location around the body, reproducibly maps to excitation of neurons at a specific location in the cortex, and therefore, to the surrounding area of the Reciprocal Domain. This suggests that if the Reciprocal Domain is the mind, then either it, or the neurons of the brain, or the combination of the two, must be able to detect local changes in the electrochemical flux, caused by those local changes in neuronal activity. This process should also be able to distinguish between changes in neuronal activity at different sites, which are experienced as different sensations. A candidate mind has to be unified, but not uniform: it has to be spatially differentiated – spatially aware – because it has to map the neural activity of the higher brain, and thereby the body, through localized changes within this single entity.

The intensity of a sensation is the frequency or pattern of the neuronal action potentials, rather than action potentials, rather than any increase in the amplitude of each depolarisation. It is an all-or-none depolarisation. It is an all-or-none system. A “spike train” (a rapid succession of action potentials) succession of action potentials) causes repeated changes in the extracellular concentrations of extracellular concentrations of cations, as the sodium and potassium ions cross the plasma membrane cross the plasma membrane of the stimulated neurons. It is already appreciated that this causes the

appreciated that this causes the potential difference across the plasma membrane of the excited membrane of the excited neurons to fluctuate rapidly, but it also causes localized, rapid changes in the localized, rapid changes in the electric field in this region of the Reciprocal Domain. This local Reciprocal Domain. This local oscillation in the electric field in the Reciprocal Domain is a physical Reciprocal Domain is a physical event that might affect the rest of this space, or other parts of the space, or other parts of the brain. We may, perhaps, tentatively conjecture that this putative mind is that this putative mind is changed by, or detects, the localised oscillation in the electric field within the oscillation in the electric field within the brain, which we experience as a particular sensation at a a particular sensation at a specific site of the body. The mind must be informed about the sensory informed about the sensory stimulus from the intensity, the site and duration of the change in the duration of the change in the Reciprocal Domain caused by the local neuronal activity. Our subjective neuronal activity. Our subjective experience of sensations and perceptions comes from those three comes from those three factors alone. Some may consider this a model of the mind as a homunculus, mind as a homunculus, as it is a single physical entity within the brain upon which stimuli from the upon which stimuli from the sensory surfaces of the body map.

Corollaries of This Biological Model of the Mind

Other Minds

This hypothesis offers biological criteria for attributing Reciprocal Domains to other species. We can Domains to other species. We can identify organisms with similar structural features of the brain. This features of the brain. This new model predicts the structural features of the brain that are needed to the brain that are needed to envelop the Reciprocal Domain. These are essential for the creation of essential for the creation of this isolated extracellular space. So structures such as the meninges, structures such as the meninges, choroid plexus and BBB – or analogous features that perform similar features that perform similar functions – indicate that the organism has the Reciprocal Domain that is the Reciprocal Domain that is proposed to be the mind. It would appear that mammals and birds, mammals and birds, together with the rest of the vertebrates, have brains that fulfil these criteria

that fulfil these criteria {Cserr & Bundgaard, 1984}. Furthermore, invertebrates from different phyla, invertebrates from different phyla, including molluscs, such as the cephalopods (octopus, squid and cuttlefish), and some arthropods, such as crustaceans and insects, create similar structures to the BBB {Abbott, 1992}; therefore, they may create structures similar to the Reciprocal Domain.

Domain.

The Convergent Evolution of Minds

The last common ancestor of mammals, cephalopods and crustaceans – of chordates, molluscs and arthropods – probably existed in the Cambrian or Ediacaran periods. The last common ancestors would have been before the stem groups of these modern phyla. They were probably tiny hollow balls of cells, perhaps indented, with at most simple nervous systems {Beaumont, 2009}. Therefore, it is extremely unlikely that the last common ancestor of these lines would have formed an enveloped Reciprocal Domain around the neurons in a brain.

On the basis of this new model, brains with similar Reciprocal Domains enveloped around clusters of neurons seem to have evolved at least three times on Earth. This suggests that the creation of this structure was not a single, incredibly fortuitous event. The current Reciprocal Domain requires at least three structures to surround the neuronal tissue, and it would have been unlikely that these attributes arose simultaneously in three separate evolutionary lines. It appears that some of the structures that now form the envelope around the Reciprocal Domain arose before the evolution of the modern form of mind.

Reciprocal Domains in Other Organs

The structure of the brain has evolved to seal in and maintain a Reciprocal Domain around the neurons. This extracellular compartment is widely conserved across vertebrates, and a similar system seems to have evolved in some invertebrates. It is worth considering whether similar Reciprocal Domains are formed in other organs with excitable cells. This might reveal common features of the biology of these cells and organs.

The Spine

The spinal column is sheathed by a continuation of the meninges, the three membranes that envelop the brain. The blood supply to the spine is similar to the brain, in that the endothelium forms a barrier to prevent the plasma perfusing into the tissues. The interstitial fluid and cerebrospinal fluid in the spine are the same as that surrounding the neurons of the brain. It will be patterned with the counterpart to the electrochemical flux of the neurons in the same way. Axons of the sensory neurons from around the body are spatially organized within the spinal cord. This somatotopic organization of the spinal cord seems to use a similar spatial arrangement of the neuronal activity from different sites of the body, as the topographic mapping of the neo-cortex.

The Retina

The retina has a structure in which the excitable photoreceptor cells – and the neurons and glia – are the neurons and glia – are enveloped within the structure of the tissue; so that the excitable cells are that the excitable cells are surrounded by a micro-environment of fluid, which is separate from the rest which is separate from the rest of the body-fluid. The activity of the excitable cells creates an excitable cells creates an electrochemical counterpart in this fluid, which is not perturbed or mixed with

is not perturbed or mixed with the rest of the body fluid.

Peripheral Nerves

Peripheral nerves are not enveloped by membranes; however, there is a sheath of ECM – the endoneurium – around the neurons. This forms a barrier that separates the endoneurial fluid around the neuron from the rest of the body fluid. Thus, the peripheral nervous system makes a protective structure that also creates and maintains a special micro-environment around the neurons. So there is fluid-filled space around peripheral neurons that has an ionic flux that is complementary to the neurons.

Some form of Reciprocal Domain surrounds and envelops different types of excitable cells, at a number of sites, in a number of organs, in multi-cellular animals. It seems that the electrochemical flux in the extracellular domain around excitable cells is either highly conserved, or repeatedly selected. This suggests that the Reciprocal Domain around excitable cells is part of a fundamental mechanism.

In studying the brain and other organs in which excitable cells are enveloped, it will be important to consider the micro-environment around the cells that are imprinted with the counterpart of the ionic flux at the surface of the excitable cells. The preparation of excitable cells for study *in vitro* may remove the enveloping structure that make and maintain the Reciprocal Domain, which might create an artefact. The preparation of tissue samples for microscopy may dehydrate them, and misrepresent the space around the neurons.

Bio-Medical Corollaries of This Model of the Mind

Abnormal Brain Architecture

Individuals can live with brains with strikingly atypical morphology, due to developmental anomalies, injury or surgery. For example, hydrocephaly can cause some people to lose a considerable amount of neural tissue from the cortex, but this does not necessarily cause devastating mental problems. In this condition, the ventricles of the brain do not drain properly during development, so they expand, exerting pressure on the surrounding tissue. The reduction in neuronal tissue can be considerable, with some cases reporting more than a 70% loss of cortex {Feuillet *et al.*, 2007}.

If the mind is conceived of as, in some sense, just the network of neurons in the brain, or an emergent property of them, then the health of such individuals seems inexplicable. However, this apparent paradox may derive from a misleading analogy: brains are sometimes thought to be like – to be functionally equivalent to – contemporary digital computers. Modern microprocessors are manufactured to extremely high standards of accuracy because the components have to be perfect to function at all. Their construction has to be precise because the circuitry does not tolerate changes. The precision of synthetic circuitry is different from the growth of biological organs, in which neurons can grow differently in each brain. If we conceive of the Reciprocal Domain as the mind, then it does not necessarily depend upon interacting with a certain specific map of neurons, and the ability of each mind to function around its own network of neurons is less surprising. This idea suggests that individuals with very different numbers and arrangements of neurons may thrive. Nevertheless, this model predicts that the

predicts that the structural features that envelop the Reciprocal Domain within the brain are present within the brain are present and intact in everyone.

Consciousness

This biological model proposes that a continuous extracellular realm enclosed within the brain is the mind. This Reciprocal Domain is essential for the individual, as the brain would not work if its integrity were compromised. This model contrasts with the idea that it is conceivable that individuals could have physically identical brains, and act normally, without being conscious {Chalmers, 1996}. This new biological model of the mind predicts that it is not possible for individuals to live and act without a viable Reciprocal Domain; they would simply be unconscious. The human brain has evolved to function with two interacting parts: the network of neurons and the Reciprocal Domain.

Disruption of the Mind

Physical Trauma

Traumatic brain injury (TBI) is usually thought to occur due to injury to the neurons or the disruption of their connections. The new hypothesis offers an alternative mechanism: the structural elements of the brain that surround the Reciprocal Domain are vital, but they may be vulnerable to physical disruption, which might occur independently from neuronal injury. The physical integrity of this envelope is crucial to maintain the isolation of the electrochemical flux in the micro-environment around the neurons. So injury and disruption of the structures that envelop the neurons of the brain could compromise the Reciprocal Domain, and may cause brain dysfunction, independently from injury to the neurons.

Intoxication

Neurons are susceptible to alcohol; therefore, research often focuses upon the responses of these cells to drugs. Nevertheless, this new model suggests another possible mode of action: drugs such as ethanol might partially compromise the integrity of the structures that envelop the Reciprocal Domain on a temporary basis, and thereby intoxicate the mind. For example, ethanol could disrupt either the plasma membrane of, or the tight junctions between, the endothelial cells that comprise the BBB. This might lead to the contamination of the enclosed micro-environment around the neurons by the circulation.

The Reciprocal Domain and Some Disorders of the Mind

Mental illnesses tend to be considered as disorders that primarily affect the neurons of the brain; however, in light of the new model, perhaps mechanisms affecting the Reciprocal Domain could be implicated in some conditions. For example, early symptoms of some forms of dementia may present before pathological changes to the neurons can be detected. In some cases, this might be due to the deterioration of the brain structures that maintain the Reciprocal Domain. This might lead to the Reciprocal Domain no longer being kept separate from the circulation. For example, the integrity of the BBB could become compromised through age-related degeneration of the vasculature.

The brain is much physically softer than other organs because it does not have much of the tough, fibrous ECM found in other organs. This leaves the brain vulnerable to injury, but it enables the interstitial fluid to surround, and flow around, the neurons.

surround, and flow around, the neurons. A possible explanation for the early stages of some types of early stages of some types of mental decline could be a reduction in the permeability of the Reciprocal permeability of the Reciprocal Domain. For example, the accumulation of extracellular proteins or extracellular proteins or peptides in precipitates or plaques may hamper the free movement of the the free movement of the interstitial fluid around the Reciprocal Domain, before there is any harm to before there is any harm to the neurons.

This Hypothesis Is Empirically Testable

It should be possible to test empirically some of the corollaries of this model of the brain against others. This should distinguish between this model – of direct and indirect influences upon neurons – and models that only consider direct interactions between neurons. A first test could be to try to disrupt the Reciprocal Domain – without changing neuronal activity – to discover whether this changes the experience of the volunteer. This type of procedure would be predicted to uncouple neuronal activity from the mental events that usually accompany it.

It may be possible to disrupt the link between a specific neuronal activity in the brain and the in the brain and the associated experience of the subject. Briefly, assuming that neuronal correlates of assuming that neuronal correlates of sensations can be found, it may be possible to physically locate possible to physically locate and reach such neurons whilst the volunteer remains conscious. It may remains conscious. It may be possible to perfuse the micro-environment around the specific neurons around the specific neurons whilst exposing the patient to the stimulus. The aim will be to gently The aim will be to gently perfuse around the cell, without disrupting the spikes associated with the spikes associated with the stimulus, as one can gently blow on a candle and move the air around the move the air around the flame – without extinguishing it – to disrupt the link between the characteristic link between the characteristic neuronal activity and the complementary ionic flux in the micro-

ionic flux in the micro-environment. This procedure would be predicted to disrupt the phenomenal
disrupt the phenomenal experience that is normally associated with this neuronal activity.
neuronal activity.

Comparison with Other Ideas About the Mind and the Self

This new biological hypothesis of the enveloped Reciprocal Domain of the brain as the mind has points of contact – and contrast – with other ideas about the nature of the brain and mind. For example, this is a very different conception of the brain and mental events from the one sought in projects to discover “neural correlates of consciousness” (NCC). Such studies are typically designed to scan for regions of the brain that become more active, as indicated by an increase in blood-flow, or another biophysical marker of a local increase in metabolism, when a volunteer is performing a task (compared to the control, of not performing that task). The argument runs that NCCs are the minimal events, or changes, in the brain that occur when specific mental events occur, so that this neuronal activity somehow correlates with consciousness of this task or experience. This experimental design rests upon the tacit assumption that regions of the brain that do not consistently change when a particular task is undertaken are not contributing to the process, like electronic components on stand-by. In contrast, the new model emphasizes that resting potentials, and apparently random spikes, contribute to the whole Reciprocal Domain within the brain, and create and maintain this domain, in which specific changes are caused by local increases in neuronal activity.

This new hypothesis is different from models of the brain as “nothing but a pack of neurons”, and mind pack of neurons”, and mind as an emergent property of the network of them. The neurons are

The neurons are essential; but the structural basis of the brain is also vital, including the features that vital, including the features that enclose, and thereby create, the novel Reciprocal Domain. The BIF is Reciprocal Domain. The BIF is essential for neuronal function, as the neurons could not create resting neurons could not create resting and action potentials if they were not correctly spaced. The activity of correctly spaced. The activity of the neurons has been interpreted as the brain performing brain performing computation, processing information as a logical circuit, without the indirect influence without the indirect influence of the Reciprocal Domain. However, as Searle has pointed out, the has pointed out, the operation of an algorithm or computation alone is insufficient to create syntax or insufficient to create syntax or semantics. It is crucial that there is an “outside interpreter who assigns “outside interpreter who assigns a computational interpretation to the system” {ref: Dennett & Searle, system” {ref: Dennett & Searle, 1995}. This role could be filled by the Reciprocal Domain.

Reciprocal Domain.

This new model of the mind comprises of two counterparts: the network of neurons and the Reciprocal Domain. The proposal of two interacting domains is similar to some versions of dualism, but it is not necessary to conjure up a non-material mind for the new model, nor fret about the interaction between the material brain and an immaterial mind.

Tononi has postulated a mechanism, or process, is necessary to integrate the “differences that make the “differences that make a difference” in neural activity in the brain, in his Integrated Information in his Integrated Information Theory (IIT) {Tononi, 2008}. He suggests that human consciousness has human consciousness has to be a single entity that integrates all the information from neuronal inputs, information from neuronal inputs, and which has a repertoire of differentiated states. He suggests that differentiated states. He suggests that this integration stems from the networking of the neurons; but networking of the neurons; but the Reciprocal Domain, with its localized fluctuations in an entity that

fluctuations in an entity that already exists, caused by changes in neuronal activity, fulfils a similar role neuronal activity, fulfils a similar role in this new hypothesis.

Searle has proposed a *unified field* model as the biological basis of the mind {Searle, 2000}. That is, neuronal correlates of mental events are necessary, but not sufficient, to account for phenomenal experience. Sensations or experiences take place as an excitation (or change) in a pre-existing *field* of consciousness. Searle suggests that this unified field is based upon neurons, or an emergent property of networks of them; however, in many other respects, the extracellular Reciprocal Domain fits with this idea: a part of the brain that persists – which is constantly altered by the activity of neurons – which can also change the activity of efferent neurons.

Summary

This account describes the cationic flux in the fluid in the enclosed extracellular space within the brain, and hypothesises about the nature and consequences of this novel biology. This manuscript comprises of three linked parts: the discovery of the Reciprocal Domain and the description of its implications; the hypothesis that the electrochemical activity in this space within the brain could be the core self, or mind; and thirdly, the tentative conjecture that our phenomenal experiences may be the rapid fluctuations in the electric field caused by the cationic flux.

The discovery of the Reciprocal Domain within the brain is the first part of this work. This identification of this work. This identification is built upon long-standing evidence. The Reciprocal Domain is The Reciprocal Domain is enclosed by structures that envelop the BIF around the neurons. The BBB

the neurons. The BBB was identified over 100 years ago, and the meninges were discovered were discovered centuries ago. The composition of the BIF indicates that it is distinct from the plasma is distinct from the plasma and other body fluids. Hodgkin & Huxley discovered the orthogonal discovered the orthogonal movement of ions across the neuronal plasma membrane around the membrane around the middle of the 20th Century.

The attributes that encourage the hypothesis that this Reciprocal Domain is the core self, or mind are: this Reciprocal Domain is a unified entity that is spatially defined by surrounding – and being surrounded by – all the cells of the brain, including the neurons, within the brain. The cationic flux in this *inverse cell* is altered at particular sites by changes in the activity of specific neurons, which also creates local changes in the electric field. This Reciprocal Domain is a biological entity that endures through life; it could be vulnerable to chemical and physical factors that are known to alter the mind. A process has been outlined by which this Reciprocal Domain could influence neuronal activity; this could create extraordinarily complex feedback, which suggests that this part of the brain could modulate the apparently rigidly determined behaviour of networks of neurons.

Can this account of the Reciprocal Domain satisfactorily explain our experience, our sensations, or experience, our sensations, or does an “explanatory gap” remain? Well, this initial model is simple, but initial model is simple, but hopefully not over-simplified. It should be possible to investigate empirically possible to investigate empirically the nature, activity and influence of the cationic flux – and any role the cationic flux – and any role for the electric field – in the Reciprocal Domain. It will be possible to Domain. It will be possible to test and develop these initial ideas. This new model of a Reciprocal new model of a Reciprocal Domain in the brain may have implications for a broad range of ethical and

broad range of ethical and practical matters, which will require careful consideration.
consideration.

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