An Integrated Model of Brain Structure and Function

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Abstract: The fluid in the extracellular space around the neurons and glial cells is enclosed within the brain, kept separate from the circulation and the rest of the body-fluid. This brain interstitial fluid forms a distinct compartment: a sponge-like “inverse cell” surrounding, and surrounded by, all the cells of the brain. During resting and action potentials, sodium and potassium ions shuttle between the interior of the neurons and this “Reciprocal Domain” within the brain. The extracellular flux of ions is the counterpart to all the neuronal electrochemical activity (having the same intensity and duration, at the same sites in the brain), so a complementary version of all that potential information is integrated into this negative space within the brain. This flux of cations in the Reciprocal Domain may indirectly influence neuronal activity in the brain, creating immensely complex feedback. This complementary realm is unified, and exists continuously throughout life. This model identifies which species have a Reciprocal Domain, and how many times similar systems evolved. It could be vulnerable to disruption by chemical insult, traumatic injury or pathology. These are key characteristics of our core experiential selves; which encourages the idea that this Reciprocal Domain is essential for the integrated function of the brain. This model is developed and explored here.

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1. Introduction

In this manuscript, I consider the structural and functional biology of the brain, looking at how the neurons, and their electrochemical activity, may shape and affect 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 suggest how the neuronal activity of the brain is effectively integrated, creating our selves and our experiences. I propose that the functions of the brain spring from the interactions between two distinct – but complementary – biological parts: the network of interacting neurons, and the Reciprocal Domain.

2. Background

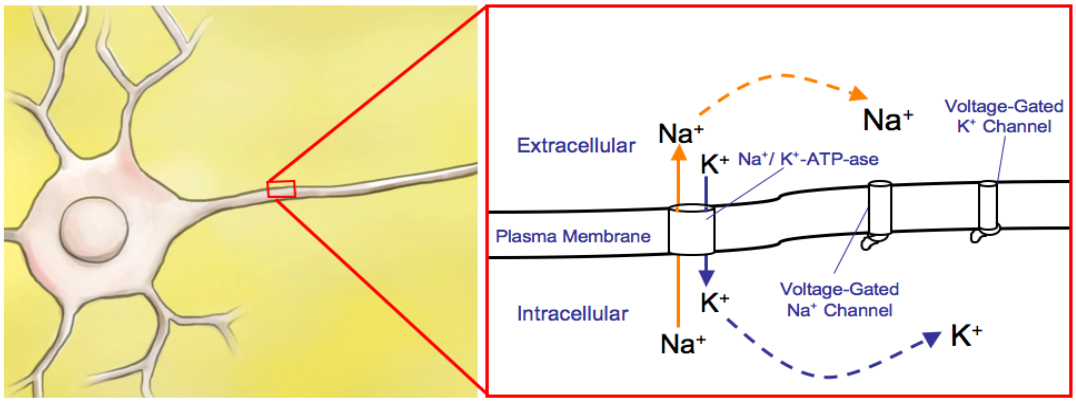
The neurons are the cells in the brain that attract the most interest. For example, the distinguished thinker Francis Crick summarized his *Astonishing Hypothesis*, in a pastiche of Lewis Carroll, as, "You're nothing but a pack of neurons" {Crick, 1994}. The human brain contains around 10^{11} neurons; 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 crankshaft move; but their activity can only be understood within the context of the whole engine; therefore, this study will try to consider the neurons, and their activity, within the wider biology of the brain.

2.1 A Sketch of Neuronal Electrochemical Activity

Neurons are not electronic. Unlike solid-state electronic components, to which they are sometimes misleadingly compared, neuronal activity is not based upon the movement of electrons from one end to the other. The processes of neuronal excitation were discovered in the middle of the 20th Century: Briefly, the Hodgkin-Huxley model describes the excitation of neurons based upon the movement of ions across the plasma membrane into and out of the cell {Hodgkin & Huxley, 1952}. Neurons use metabolic energy to pump ions across the plasma membrane, creating a resting potential at their surface {Figure 1}. Sodium ions (Na^+) are pumped out of the neuron cytoplasm, in exchange, potassium ions (K^+) are pumped into the cytoplasm from the extracellular fluid. Both species of ions are transported across the plasma membrane against their concentration gradients, by a protein called the Na^+/K^+-ATPase (Figure 1). The concentrations of these cations are different inside the cell, compared with the outside, which polarizes the membrane. During the resting potential, there is more than 10 times the concentration of sodium ions immediately outside the cell compared with inside, and around 20 times more potassium ions inside the cell than outside {Hodgkin, 1958}. This process requires metabolic energy. The brain uses a disproportionate amount of metabolic energy (approximately 20% of total energy consumed by roughly 2% of adult body weight) because the neurons 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 – occurs when sodium ions flood back across the plasma membrane into the neuron, and then potassium ions pass back out of the cell into the surrounding micro-environment {Figure 2}. These movements are passive, in that they do not require metabolic energy, as the ions travel down their concentration-gradients and equilibrate across the membrane, through specific ion channels. The ion channels are reversibly gated trans-membrane proteins: they change conformation in response to local changes in the voltage across the membrane. This opens an aqueous pore across the membrane that allows specific ions to flow across it. The flux of ions across the plasma membrane, both into and out of the cell, changes the voltage across it, which triggers the opening of nearby voltage-gated ion channels. Thus the depolarization of the plasma membrane at one point triggers the neighbouring region to depolarize, and so on. This trigger only proceeds in one direction along the membrane, as channels are not receptive to triggering for a few

milliseconds after having been open. This type of activation moves along the neuron as a metachronal – rather than synchronous – wave; the impulse travels along the surface of the neuron from the dendrites along the axon. An analogy with the propagation of an action potential along the neuronal plasma membrane is the "Mexican wave" in sports stadiums, where the wave travels around the crowd as individuals quickly stand up and sit back in their own seats, triggered by the same action of their neighbour just before them. The wave rushes around the stadium; but the spectators do not. Similarly, the wave of depolarization runs along the membrane of the neuron, as ions flow into and out of the cell, rather than charged particles flowing along the interior of the cell.

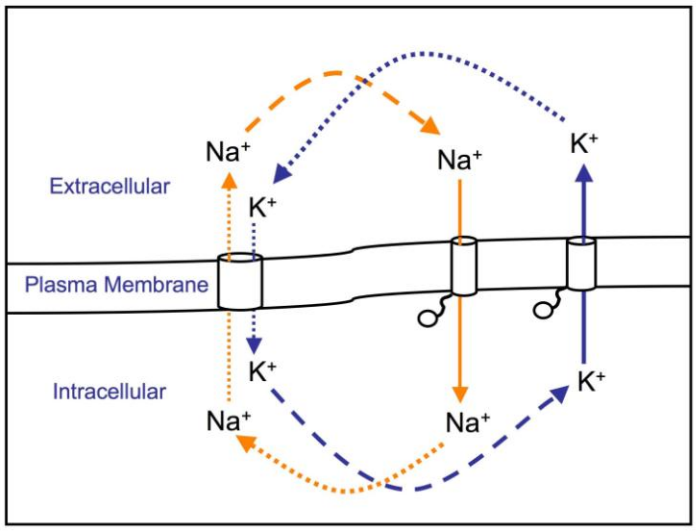


Figure 2: The action potential occurs when the gated ion channels briefly open. This depolarises the membrane as sodium ions (Na^+) and then potassium ions (K^+) equilibrate across the plasma membrane. This causes a spike, or change, in the potential difference across the plasma membrane, which triggers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

The excitation of one neuron can trigger the excitation of a neighbouring neuron. This stimulation

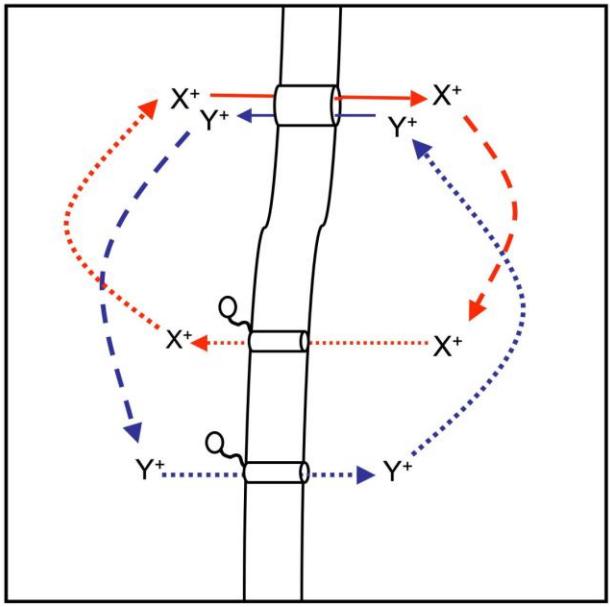
may be electrical, via electrical contact across gap junctions, or chemical transmission across a synapse. The fusing of intracellular vesicles with the plasma membrane at the synapse releases neurotransmitter into the synaptic cleft is triggered when the rate and pattern of action potentials reaching 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 components, or non-excitable cells. Neurons use metabolic energy to pump sodium and potassium ions across the plasma membrane, polarizing it, and creating a resting potential. Upon stimulation, the ions pass through specific gated ion channels in the plasma membrane, down their electrochemical gradients, creating an action potential. This changes the voltage across the plasma membrane of the neuron, which in turn affects the voltage across the neighbouring region of the neuronal membrane, which opens further voltage-gated ion channels, leading to further depolarization, and so forth. Thus, a metachronal wave of depolarization, rapidly followed by repolarisation, travels along the membrane of the neuron from the dendrites, across the cell body, and along the axon. Physical particles, such as electrons, do not "flow" through the cell to create a current; it is not a tube or wire. As the wave of excitation travels along the neuron, the movement of ions across the plasma membrane is at right angles (orthogonal) to the direction of the nerve impulse along the membrane of the neuron. The amplitude of the impulse travelling along the neuron is determined by the local gradients of ions across the membrane. Providing that there is a sufficiently large electrochemical gradient, then the wave of depolarization propagates along the neuron, in an "all-or-none" system. The pattern and rate at which impulses reach the synapse, rather than their amplitude, determine whether neurotransmitter is released at the synapse, in another "all-or-none" system.

3. Neuronal Activity Creates a Complementary Change in the Brain

The preceding brief account of the Hodgkin-Huxley model of neuronal excitation introduces the subject. The cross-sectional diagrams in Figures 1 & 2 show the movement of cations into and out of the neuron; but these illustrations can also be looked at in another way: they might be seen as showing the corresponding movement of ions into and out of the micro-environment surrounding the neuron. The similarities between the fluxes on both sides of the plasma membrane become apparent if the illustration is rotated through 90° – and the labelling simplified so that the cations are unspecified – then we may see that the fluxes of ions on the two sides of the membrane in a cross-sectional illustration appear to be similar {Figure 3}. Upon examination, we can see that the ionic fluxes on the two sides of the plasma membrane are not the same; they are complementary. That is, as an ion leaves one side of the membrane, it crosses the plasma membrane, and appears on the other side. There is one less of those ions on one side, and one more on the other. Thus, the two sides of the membrane may be considered as part and counter-part – in the sense that fossils in sedimentary rock may cleave into two complementary forms: one side convex, the other concave. They both have the same pattern, or information, at the same site; however, the part and counterpart are complementary impressions 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.



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. There are two complementary – but interacting – ionic fluxes in the brain, on either side of the neuronal plasma membranes: the intracellular part determines whether neuronal spikes propagate, and neurotransmitter is secreted, in all-or-nothing processes; but the extracellular counterpart cationic flux has not been considered yet.

3.1 The Structure of the Brain Creates a Realm that is Complementary to Neuronal Activity

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-

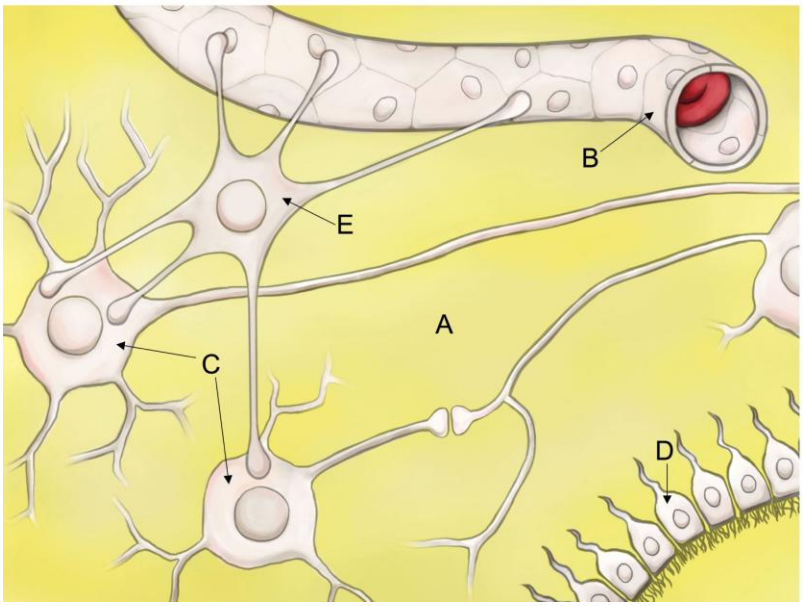
environment around the cells in most other organs are constantly perfused by fluid from the blood plasma, bringing nutrients and removing waste. So the circulation might be expected to constantly refresh the micro-environment around the neurons; however, the structure of the brain prevents this: The 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 20th Century, Ehrlich and Goldman found that stains perfused through the blood vessels of the brain do not permeate the tissue and stain the surrounding cells. Unlike in most other organs, fluid and small molecules cannot flow freely from the lumen of the cerebral blood vessels into the surrounding tissues of the brain. This separation of the circulation from the brain tissue is due to the blood-brain barrier (BBB). It has subsequently been discovered that, in mammals, the endothelial cells that line the blood vessels bind each other via tight junctions that prevent even small hydrophilic molecules from passing between these cells. This effectively seals the vessels, stopping the nutrients and ions of the plasma simply washing out from the lumen of the vessel, over the surrounding neurons. The nutrients and ions have to be transported across the membranes of the endothelial cells, either into the brain interstitial fluid, or directly to the neurons via astrocytes.

The meninges, choroid plexus and BBB combine to form an envelope, or barrier, around the brain,

which isolates it from the rest of the body. The brain interstitial fluid (BIF) that surrounds the cells of the brain, including the neurons, is distinct from the plasma of the circulation. It has a much lower protein concentration, and few circulating cells. Nevertheless, it does contain some nutrients, neuromodulators and inorganic ions. It flows slowly around the brain, without mixing with the blood. The BIF micro-environments around the neurons of the higher brain form a continuous entity: a unified "Reciprocal Domain" within the brain. This Reciprocal Domain might be considered as the *Negative Space*, which 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 evolved to maintain the neurons in a constant environment, away from fluctuations in the blood-levels of nutrients, ions and hormones. Such an 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 envelop the neurons and the surrounding BIF within the brain, creating this Reciprocal Domain.

4. Is the Reciprocal Domain Just an Epiphenomenon, Or Does It Have a Function?

Changes in the Reciprocal Domain considered so far could just be 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 function of the brain; however, if it is found that changes in this extracellular space within the brain could exert some effects upon brain activity, then it would surely warrant further exploration. This possibility is considered in the following sections.

4.1 The Reciprocal Domain and Perception

Current theories of perception focus upon the neuronal pathways 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 leads to 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 integrated model of brain structure and function 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 simultaneously causes electrochemical flux in the Reciprocal Domain around those particular neurons. A neuronal correlate of sensation creates a complementary electrochemical change – at the same specific location – in the Reciprocal Domain, a larger entity shaped around all the cells in the brain. Thus, the Reciprocal Domain is patterned with a version of all the information from the neuronal activity in the brain. Perhaps this would be expected of the experiential centre of the brain?

4.2 Can 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

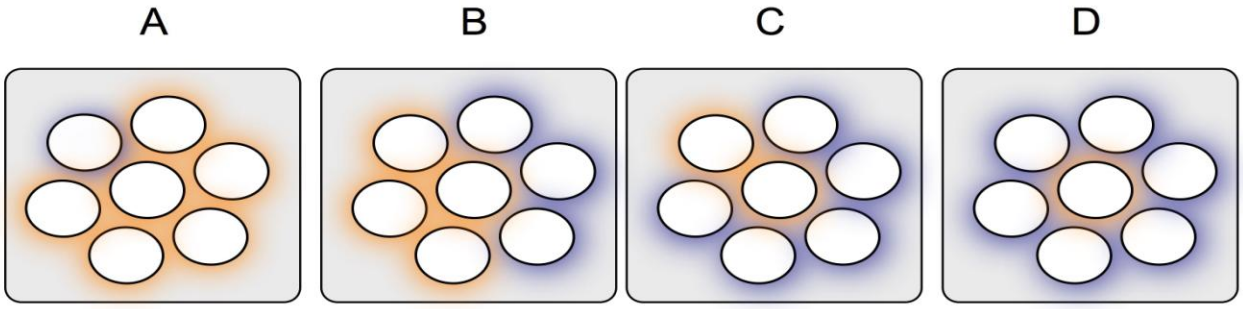
upon neuronal activity: neurons are here designated to have a direct influence upon each other via synapses or gap junctions. These are the classical methods of neuronal stimulation and inhibition. The Reciprocal Domain will be considered to have an indirect influence upon neurons if changes in the extracellular electrochemical flux can alter their activity.

The lack of a substantial collagen-rich extracellular matrix (ECM) in the brain brings the 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 points all 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 Figure 5. A cluster of neurons is shown in cross-section, indicating where the micro-environments around the neuronal 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 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 when they coincide.

This indirect influence of the Reciprocal Domain upon neuronal activity at first may seem implausible because action potentials of several neurons will have to coincide around a particular region of a neuron. However, the brain contains tens of thousands of millions of neurons, producing action potentials sporadically, randomly 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 topographic mapping of the motor cortex, this may begin to

explain how we initiate movements and actions.

The indirect influence of neuronal cationic flux upon the electrochemical activity of neighbouring neurons is not a classical form of neuron-neuron communication. During indirect influence, excited cells do not affect other cells by secreting small organic molecules, which diffuse across the extracellular space between cells, and bind specific receptors. Nevertheless, it does seem to be a case of volume transmission {Agnati *et al.*, 1995} because neuronal activity causes a change – a flux of cations in the extracellular BIF micro-environment – that may alter the activity of neighbouring neurons.

On the other hand, when the extracellular *Negative Space* between the neurons, which is enveloped within the brain, is considered as an "inverse cell" – the Reciprocal Domain – then this entity is more than just the gap between cells across which neurotransmitters and neuromodulators diffuse. This Reciprocal Domain is an integral part of the brain, and is essential for brain function. It is shaped around all the cells in the brain. It is in intimate contact with them; it surrounds them, as they surround it. This inverse cell is bounded by the mosaic of plasma membranes of all the neurons and other cells in the brain. The excitability of brain tissue necessarily involves the movement of ions across these plasma membranes between the neurons and the Reciprocal Domain. This Reciprocal Domain integrates a complementary version of all the electrochemical fluctuations; amongst a number of attributes, the cationic flux within this complementary realm may indirectly influence the activity of neurons.

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.

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 imply that efferent activity is not completely determined by afferent activity? The propagation of any particular action potential will be directly influenced and triggered by the activity of the neurons in the network, but will also be indirectly influenced by the electrochemical flux that is integrated into the Reciprocal Domain, and the recursive feedback loops between the two realms. The propagation of any specific action potential cannot be predicted with certainty,

unless the activity of all the integrated neurons at that particular instant is known – and thereby the indirect influence of the Reciprocal Domain – which is beyond measurement or computation. Perhaps we should say that the interaction of direct and indirect influences creates such enormous complexity in this biological system that the integrated whole is beyond calculation? The brain seems to be a deterministic system; but – in practice – it is beyond accurate measurement and calculation, limiting our knowledge and ability to predict its activity with certainty.

5. Implications of the Reciprocal Domain for the Brain

This Reciprocal Domain could be an important piece of the brain. It is an entity that is created and shaped by the structure of the brain, and patterned by the activity of all the neurons. It is electrochemically 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. This complexity could make the network of neurons in the brain more responsive and flexible than the role of information processor that has previously been assigned to it. These are properties that we might reasonably associate with the experiential core, which raises the question: could the Reciprocal Domain be the experiential centre, the core self?

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

should form a unified whole so that it can engage with – experience – sites of neuronal activity all around the brain, often simultaneously, 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 brain injury 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 us, 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 self. This idea shall be developed and explored.

5.1 An Integrative Model of Brain Structure and Function

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 counterpart to all the neuronal activity is integrated into this space. Importantly, both the resting and action potentials contribute to this electrochemical flux. This creates an entity that exists continuously – although it is constantly changing – throughout the

life of the individual. Local changes in neuronal activity, such as "neuronal correlates of sensations" triggered by stimulation of the senses, change the ionic flux in the particular region of the Reciprocal Domain surrounding those neurons. These could be specific events or experiences.

5.2 The Structure of This Reciprocal Domain

The BIF forms a continuous environment throughout the extracellular space within the higher brain, so this Reciprocal Domain is a material object with physical properties. It is topologically extremely complex, as it surrounds, and is surrounded by, all the neurons, glia and other cells in the higher brain; the boundary around this compartment is formed by the plasma membranes of all the cells within the brain. This effectively makes a single extracellular compartment – an "inverse cell" or "sponge" – around all the cells, including the neurons. This realm is separated from the rest of the body fluid. It sits within the higher brain as a unified, continuous whole; however, if this entity does experience separate neuronal activities as distinct sensations, then it cannot be uniform. It must have spatial structure for it to engage with the architecture – the spatial arrangement – of the brain.

5.21 Topographic Maps in the Brain and the Unified Non-Uniform Reciprocal Domain

The neurological pathways from a number of sensory surfaces of the body – such as the skin, cochlea and retina; along with some motor centres – project onto the brain cortices in systematic spatial order to form topographic maps of the body. Sensations from the body cause neuronal activity at the surface of the cortex in an ordered manner; neighbouring parts of the body map onto adjacent areas of the brain. This topographic mapping in the CNS raises tantalizing questions, and provokes ideas, about the nature of the brain and our experience of our bodies and through our senses, the world, and the interaction between them: why have topographic maps repeatedly

evolved for the perception of different senses? Why are there similar maps for both sensory and motor systems? These topographic maps indicate that the brain is spatially organized; the site of the body where the stimulus originates can be inferred from the site of the change in neuronal activity induced in the cortex. Topographic mapping seems to imply that there has to be some entity that detects or "reads off" the site of change in neuronal activity from the topographic map. This suggests that the entity that experiences the variety of our sensations is also extended in space, about the size of the brain, and able to detect and distinguish changes in neuronal activity at different sites all over the brain.

The new model of the Reciprocal Domain as the entity that integrates – and experiences – the activity of the neurons, begins to explain the topographic mapping of the brain, as topographic mapping can tell us about the nature of this negative space in the brain. 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 does experience our sensations, 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. Any candidate integrated experiential Self 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 space.

The intensity of a sensation is the frequency or pattern of the neuronal action potentials, rather than any increase in the amplitude of each depolarisation. It is an all-or-none system. A "spike train" (a rapid succession of action potentials) causes repeated changes in the extracellular concentrations of cations, as the sodium and potassium ions cross the plasma membrane of the stimulated neurons. It is already appreciated that this causes the potential difference across the plasma membrane of the excited neurons to fluctuate rapidly, but it also causes localized, rapid changes in the electric field in this region of the brain. This local fluctuation in the electric field, around the active neurons, is a physical event that might affect the rest of this space, or other parts of the brain. We may, perhaps, tentatively conjecture that this area of the Reciprocal Domain is changed by, detects, the localised change in the electric field within the brain, which we experience as a particular sensation at a specific site of the body. The integrated Self that experiences sensations must be informed about the sensory stimulus by the intensity, the site and duration of the change in the Reciprocal Domain caused by local neuronal activity. Our subjective experience of different sensations and perceptions derives from these three factors. Stimuli get their particular sensation or *feel* from where they occur in the Reciprocal Domain.

6. Corollaries of This Integrative Model of Brain Function

6.1 Reciprocal Domains in Other Species

This integrative model of brain function offers biological criteria for attributing Reciprocal Domains to other species. We can identify organisms with similar structural features of the brain. This new model predicts structural features of the brain that are needed to envelop the Reciprocal Domain. Anatomical structures that perform these roles are essential for the creation of this enveloped extracellular space. So structures such as the meninges, choroid plexus and BBB – or analogous features that perform similar functions – indicate that the organism has the Reciprocal

Domain that is proposed to be the experiential core, or self. It would appear that mammals and birds, together with the rest of the vertebrates, have brains that fulfil these criteria {Cserr & Bundgaard, 1984}. Furthermore, 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 have structures similar to the Reciprocal Domain.

6.11 The Convergent Evolution of Reciprocal Domains

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 such structures was not a single, incredibly fortuitous event. The current Reciprocal Domain requires at least three anatomical structures to surround the neuronal tissue, and it would have been unlikely that these features arose simultaneously in three separate evolutionary lines. This suggests that some of the structures that now form the envelope around the Reciprocal Domain arose before the evolution of the modern function of the Reciprocal Domain.

6.2 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.

6.21 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 that prevents plasma perfusing the tissues. The interstitial fluid and cerebrospinal fluid in the spine are similar to 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.

6.22 The Retina

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

6.23 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 several 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 distort the space around the neurons.

6.3 Bio-Medical Corollaries of This Integrated Model of the Functional Brain

6.31 Abnormal Brain Architecture

Individuals can live with brains that have 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}.

When the core self is conceived of as, in some sense, just the network of neurons in the brain, or an emergent property of them, then the vitality of these 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 may grow differently in each brain. If we conceive of the Reciprocal Domain as the experiential core, then it does not necessarily depend upon interacting with a single specific "circuit" of neurons, and the integration of each brain 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 structural features that envelop the Reciprocal Domain within the brain are present and intact in those who are conscious.

6.32 Consciousness Requires the Reciprocal Domain

This new biological model proposes that the functions of the brain are the complementary electrochemical activities of the network of neurons and the Reciprocal Domain. These parts of the

brain are intimately linked, and both are necessary. An individual without an intact Reciprocal Domain would not be conscious; their brain simply would not function. Furthermore, this model does not require any mysterious additional ingredient to explain brain function: the network of neurons arranged together with the Reciprocal Domain are sufficient. Our self, our sensations and – through our senses – our experiences of the world, are electrochemical in nature.

6.4 Disruption of the Reciprocal Domain

6.41 Physical Trauma

Traumatic brain injury (TBI) is usually thought to occur due to damage 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.

6.42 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 individual. 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.

6.42 The Reciprocal Domain and Pathological Changes in the Brain

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

7. This Integrated Model of Brain Function Is Empirically Testable

It should be possible to test empirically some of the corollaries of this integrated model of brain function 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 specific neuronal activity in the brain and the associated experience of the subject. Briefly, assuming that neuronal correlates of sensations can be found, it may be possible to physically locate and reach such neurons whilst the volunteer remains conscious. It will be technically challenging, but it may be possible to perfuse the micro-environment around the specific neurons whilst exposing the patient to the stimulus. The aim will be to gently perfuse around the cell, without disrupting the spikes associated with the stimulus, as one can gently blow on a candle and move the air around the flame – without extinguishing it – to disrupt the link between the characteristic neuronal activity and the complementary ionic flux in the micro-environment. This procedure would be predicted to disrupt the phenomenal experience that is normally associated with this neuronal activity.

8. Comparison of This Integrative Model of Brain Function with Ideas About the Mind

This new biological hypothesis of the enveloped Reciprocal Domain as essential for the integrated function of the brain has points of contact – and contrast – with various ideas about the nature of the mind and its relation to the brain. 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 unused electronic components on stand-by. In contrast, the new model emphasizes that resting potentials, rhythmic 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 changes in neuronal activity.

This new hypothesis is different from models of the brain as "nothing but a pack of neurons", and the mind as an emergent property of the network of them. The neurons are necessary; but the structural basis of the integration of the brain is also crucial, including those features that enclose, and thereby create, the novel Reciprocal Domain. The BIF is essential for neuronal function, as the neurons could not create resting and action potentials if they were not correctly spaced. The activity of the neurons has been interpreted as the brain performing computation, processing information as a logical circuit, without the indirect influence of the Reciprocal Domain. However, as Searle has pointed out, the operation of an algorithm or computation alone is insufficient to create syntax or semantics. It is crucial that there is an "outside interpreter who assigns a computational interpretation to the system" {Dennett & Searle, 1995}. The Reciprocal Domain may fulfil this role.

This integrated model of brain function consists of two counterparts: the network of neurons and the Reciprocal Domain. The proposal of two interacting domains might seem reminiscent of some versions of dualism; however, it is not necessary to conjure up a non-material mind for the new model, nor fret about the interaction between material neurons and an immaterial mind.

Tononi has postulated a mechanism, or process, is necessary to integrate the "differences that make a difference" in neural activity in the brain, in his Integrated Information Theory (IIT) {Tononi, 2008}. He suggests that human consciousness has to be a single entity that integrates all the information from neuronal inputs, and which has a repertoire of differentiated states. He suggests that this integration stems from the networking of neurons; however, the Reciprocal Domain, where neuronal activity causes localized fluctuations in an entity that already exists, fulfils a similar role in this new model.

Searle has proposed a *unified field* model as the biological basis of the mind. 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. He suggests that, "what we have to look for is some massive activity of the brain capable of producing a unified holistic conscious experience" {Searle, 2000}. He suggests that this unified field is based upon the interactions between neurons, or an emergent property of networks of them; however, in many respects, the extracellular Reciprocal Domain fulfils this role: a piece of the brain that persists – although constantly altered by the activity of neurons – which may also change the activity of efferent neurons.

9. Summary

This manuscript attempts to build an integrated model of brain structure and function. I propose that the extracellular region around the neurons and other cells of the brain is a crucial part of the brain in its own right: the Reciprocal Domain. This is a new description of an encapsulated space within the body, and of brain structure and function. This compartment surrounds excitable cells

that pass cations across their plasma membranes; therefore, it bears a complementary version of all their electrochemical activity. This is the basis for the hypothesis that the electrochemical activity in the encapsulated extracellular space within the brain is the core experiential self. This outline of the new model is followed by brief sketches of some of the implications of this novel biology. In addition, a tentative conjecture is then put forward that our phenomenal experiences could be the rapid fluctuations in the electric field at specific sites, caused by the cationic flux in this enveloped extracellular space within the brain.

The description of the Reciprocal Domain within the brain is built upon long-standing evidence. The Reciprocal Domain is enclosed by structures that envelop the BIF around the neurons. The composition of the BIF indicates that it is distinct from the plasma and other body fluids. The BBB was identified over 100 years ago, and the meninges before that. Hodgkin & Huxley discovered the orthogonal movement of cations across the plasma membrane of excitable cells around the middle of the 20th Century. This flux of ions across the plasma membrane of the neurons, within a sealed compartment, creates the complementary electrochemical activity of the Reciprocal Domain.

The attributes that encourage the hypothesis that this Reciprocal Domain is the core experiential self are: this Reciprocal Domain is a unified entity that is spatially defined by surrounding – and being surrounded by – all the cells, 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 our experience. 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 integrated model of brain function – and this account of the Reciprocal Domain – satisfactorily explain our experience and sensations, or does an "explanatory gap" remain? Well, this initial model is simple, but hopefully not over-simplified. It should be possible to investigate empirically the nature, activity and influence of the cationic flux in the Reciprocal Domain – and any role for the electric field – on the function of the brain. It will be possible to test and develop these initial ideas. This new model of the integrated function of the brain could have implications for a broad range of ethical and practical matters, which will require careful consideration.

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