Computational Study of
the Migraine Aura and the Cortical Spreading Depression Phenomenon

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Abstract

The computational study of the Migraine Aura and the Cortical Spreading Depression Phenomenon is discussed in this review. A brief discussion of the relevant neurological background is given first and afterwards the existing computational models are described and criticized. The discussion is then extended in an effort to explore modifications to these models and new modeling possibilities. Finally, the outstanding questions are addressed and further research directions are proposed. It is hoped that the research on this area will eventually provide significant and multidimensional scientific insights both for the migraines disease and the overall functionality of the brain.

1. Basic Background

The migraine disease is a chronic complex disorder that is characterized by convulsive throbbing head pain, usually in one part of the head, often accompanied by negative symptoms such as nausea, vomiting, increased sensitivity to light and sound and cognitive disturbances. Patients often experience various deficits that precede the main attack and are generally called aura (i.e. problems with motor control, speech, etc.). The most common of them, experienced by about 20-30% of the patients [1, 2], is the Visual Aura.

Visual aura can be in general described by a hallucination wave that expands through the visual field of the patient, and consists of two parts: the thin, zig-zag (crescent) -shaped, scintillating edge that expands peripherally and which is commonly called the fortification spectrum, and the scotoma, an kidney-shaped area of reduced, low-contrast vision that precedes and trails the fortification spectrum (Pic. 1). The whole phenomenon is being accompanied by changes in cerebral blood flow.

Pic. 1: A sketch showing the progression of the visual aura over time. The zig-zag lines on the edge compose the fortification spectrum. The area surrounded by the latter and the dashed line is the scotoma. Please note that this drawing does not depict the colors of the first and the reduction in contrast caused by the latter. (Picture taken from [1]).

It has now been well-established [1,2, 4] that the mechanism that underlies and creates the migraine aura in real-time is the Cortical Spreading Depression phenomenon (CSD), a sustained strong depolarization wave that slowly propagates in the cerebral cortex, generating a transient and intense spiking activity, followed by a long-lasting (in the order of minutes) neural activity suppression (Pic. 2). The migraine aura is the result of CSD taking
place in areas of the visual cortex. In this case, the intense spiking activity causes the fortification spectrum, while the suppression phenomenon is responsible for the scotoma [1]. It has been found that CSD can start from the V3A area and then migrate in more anterior areas of the visual cortex [1]. An interesting fact is that even though it mainly propagates through V1, it has not been found to migrate to the V2 area. In the past, the border between V1 and V2 has been considered responsible for this [2] (more recent notions on this will be discussed later).

This cortical excitation activity is projected onto a visual hemifield by reverse retinotopic mapping, resulting to the visual disturbances of the aura. Therefore, the study of the phenomenon can shed light on the organization of parts of the cortex and the topographic mapping of sensory inputs; for example, the shape of the fortification spectrum is believed to reflect properties of the orientation map of the V1 area (e.g. the zig-zag pattern is consistent with the layout of the orientation preference cells and the pinwheel distances in V1)[5]. The overall kidney shape of the aura on the other hand is attributed to the nature of the retinotopic map itself. It is important to note here that while it has not been experimentally verified yet that CSD takes place before the migraines without aura, there is a pending hypothesis that in this case CSD might occur in clinically “silent” areas of the cerebral cortex [1].

It has been confirmed since the previous decade that one of the most crucial factors for the initiation of CSD is an increase in the extracellular concentration of potassium and that “diffusion of either potassium or glutamate (a type of neurotransmitter) or both is necessary” for the phenomenon to take place [1, 2]. Certain malfunctions are suspected to be responsible for the sensitivity of migraineurs to CSD, like cortical hyperexcitability to external stimuli due to abnormal release of excitatory neurotransmitters, alterations in the Calcium channels, insufficient or lack of habituation\(^1\) and reduced intracortical inhibition [1]. These phenomena are out of the scope of this report and therefore will not be further discussed, but the interested reader could find plenty of information in neurobiological reports concerning migraines, like [1].

Picture 2: Representation of CSD-related information based on anatomical data (BOLD – fMRI)

2. Significance of the research on the field

The computational study of various brain deficits is of extreme importance, as, apart from the obvious benefits from their study that might hopefully lead to new and more effective treatments for migraineurs, they can reveal valuable information about normal brain functions, thus elevating key concepts and mechanisms from obscurity. It is often the case in science that important facts are “invisible” to the eye of the researcher under normal conditions, while their importance emerges under problematical, not normal conditions.

The spatiotemporal and qualitative characteristics of the migraine aura can provide

\(^1\) Habituation is the phenomenon where a decrease in the amplitudes and an increase in the latencies of the evoked potentials is taking place in the nervous system under repetitive stimulation. Interestingly, this deficit seems to disappear during migraine attacks. [1]
valuable information concerning the functional organization of the visual cortex that is not yet accessible through the current state-of-the-art brain imaging techniques. This has already happened in the past: Richards had predicted in 1971 that the zig-zag shape of the fortification pattern was due to “a hexagonal grid arrangement of local orientation columns” [2], giving a good prediction almost 20 years before the true organization was eventually revealed. As there is still much to be learnt about the organization of the visual cortex, the study of CSD and the aura provides some solid ground and remains more than worthwhile.

Results from CSD and visual aura studies on the visual cortex could be later used to study the appearance of similar phenomena in other cortical areas that are not expressed to the level of being perceptible. Computational models of migraine mechanisms could lead to further predictions about phenomena that occur “silently” in other areas, and which could be of great importance for the study of migraines themselves as well as the overall cortical function.

Moreover, and as long as migraine treatment is concerned, a further important issue is that many current preventive pharmaceutical treatments aim at preventing the patient from feeling the severe pain of the migraine (like drugs that relax the blood vessels, beta-blockers etc.) without reaching the deeper migraine mechanisms. In fact, if CSD silently takes place in other cortical regions in migraines without aura as well, which is highly possible, the preventive treatments should straightly aim at preventing CSDs. Unfortunately, it is often the case that patients under preventive treatment experience less pain but the full extent of the other migraine-related deficits.

Finally, the study of CSD and the aura could lead to assumptions that could aid the research regarding later migraine phases, beyond CSD: there are lots of other important effects that take place during the main attack, like the over-heightening of the patient’s senses and the disturbances in cognitive functions, and their roots could still lay on or relate to the CSD phase.

3. Previous Work

3.1 The model of Reggia and Montgomery, 1996

A computational model of Cortical Spreading Depression along with its resulting visual aura simulations is presented in [3]. The model basically consists of a 2D network of hexagonally arranged neurons modeled under the reaction-diffusion hypothesis of Potassium ions. As it has been denoted before, an increased level of the extracellular concentration of potassium is considered to be one the most important factors for the initiation and propagation of CSD. Excitatory connections exist between adjacent neurons while inhibitory ones are considered between more distant units. The extracellular potassium concentration and the rate of insertion of the potassium ions in the cells (due to the natural tendency of the system to restore its equilibrium) are included into the activity equations of the model.

The resulting model captures the essence of the wave-like activity of CSD. The cortical activity patterns were projected back to the visual field, illustrating a periphery of intense activity in the form of patches and/or lines, spreading away from the centre of the stimulation point (where the potassium concentration had initially been increased), leaving regions of suppressed activity behind it. The simulated auras varied according to the parameter values. Two characteristic results can be seen in pictures 3 and 4. The fortification patterns are basically being formed because of front instabilities of the propagating wave [5].

The model predicts an “exponentially increasing perceived speed [of the aura] across the visual field”, which, to the best of our knowledge, has not been confirmed yet. It also has to be noted that this model does not satisfyingly capture the overall shape of the aura and especially that of the fortification spectrum. The first appears essentially circular rather than kidney shaped in the resulting images, while the latter does not show strong zig-zag patterns (and kaleidoscopic properties) and is very thick compared to the patients’ descriptions.
This could have possibly been resolved if it was feasible to incorporate and exploit orientation selectivity in the neurons of the model. An idea would be to first train the network so that it would form an orientation selectivity map. Then the response equations should be adapted to take into account the geometrical relation of the propagating activity wave and the preference selectivity of the neurons as the wave travels over the neurons.

Although the visual results fail to capture the finest details of the aura as they are commonly described by the patients, this model remains important as it provides computational evidence that CSD can underly the migraine aura. An answer that cannot be answered through this model is why and under which conditions the aura phenomenon fades away and finally disappears. This has been implicitly attributed to structural properties of the cortex by the authors [5].

A resulting example of the aural patterns produced is given in picture 6. Please notice that the kaleidoscopic nature of the fortification spectrum is again not simulated by this model. A deficit of this model, denoted by its own authors in a later paper [2] is that “the static appearance of the zigzag is still inconclusive, as similar forms would still result from orientation layouts that are arranged in linear parallel stripes”. An animated kaleidoscopic fortification spectrum was presented in [2], synthesized by the responses to the excitation wave at subsequent cortical positions.

Pictures 3 and 4: Resulting representations of the migraine aura obtained through the model of [3]

3.2 The model of Dahlem, Engelmann, Lowel and Muller, 2000

In [6], special emphasis is being put on the explanation of the zig-zag shape of the fortification spectrum and the main hypothesis tested is that this reflects the cortical organization of orientation preference. Orientation maps were created from real data by visually stimulating cats. The orientation responses were calculated for distinct patches of the orientation map as a hypothetical wave of activity propagated through the map by using the population response vector method (pic. 5). The dominant vector for all the –possibly overlapping- sub-populations of neurons was computed and the strongest response was retained.

Picture 5: Population code estimation from cortical maps (picture taken from [2])

3.3 The model of Dahlem and Muller, 2003

An approach based on a kinematical model is studied in [5] in order to simulate the propagation of the scotoma. This is a simplification over a reaction-diffusion model (as the one presented in [3]) and it models “the propagation of the wave front by considering the motion of curves with free ends”.

Picture 6: A simulation for a patch of the fortification pattern, resulting from the model of [6]
This model closely approximates the behavior of a reaction-diffusion under the condition that the medium of propagation is weakly excitable. The basic assumption here is that the velocity of the wave at any point depends only on the front curvature. As free open wave ends are also considered, tangential velocity (the rate of growth of an open end) should also be included in the model. Some simplifications have been made, e.g. that the tangential velocity is monotonously decreasing with curvature, that the medium is homogeneous and isotropic etc. but they do not seem to qualitatively affect the model, although the first simplification is being made because of the incapability of accurately relating the tangential velocity with the curvature of the wave front. The activity is mapped to the retinotopic map by a complex logarithmic function and from there back to the visual field by perspective projection.

This model manages to capture the important fact that the scotoma disappears close to the end of the visual field, after having been gradually elongated in the radial direction. The eventual failure of the aura propagation can be explained under this theoretical framework due the fact that the “convoluted surface of the cortex affects wave velocity” [5], so that the CSD waves stop for curvature-related reasons and not because of any cortical “borders”, as it had been previously suggested. Therefore, an explanation is provided about why CSD is possible to stop within V1 [2].

One could argue though that the main medium of the spiking activity propagation is the neural network itself and therefore the propagation should be essentially independent of any morphological properties of the cortex. Under this assumption, the explanation for the propagation failure presented in [5, 2] might not be sufficient or even incorrect, although the model captures some essential characteristics of CSD very well.

Another deficit of the model is that the topographic maps are not taken into account in this abstract theory, and no solid explanations are provided concerning how the fortification pattern is created, although this has been studied in a previous work of the authors [6]. Therefore, we assume that a possible combination of the two models presented in [5] and [6] would be implicitly considered suitable for providing a more complete solution (both models are re-presented together in a later work of the authors in [2]).

The paper ([5]) provides a good description and a possible explanation for the CSD propagation on the cortical surface. But then again it does not exploit topographic maps and the insights offered about other cortical mechanisms apart from CSD are limited, although the visual aura phenomenon is suitable for exploring the visual cortex deeper.

4. Outstanding Questions and Some Notions on Further Research Directions

From the discussion about the existing models and their deficits, it can be seen that none of them manages to fully serve as a holistic and complete solution for modeling the migraine aura and CSD. The model of Reggia and Montgomery takes a low level approach that uses neural networks of hexagonally arranged neurons that incorporate both inhibitory and excitatory connections. More importantly, it takes into account the potassium concentrations dynamics. Apart from the study of the activity propagation and its correspondence to an aura-like visual effect, little insight is offered about how the aura is related to the structural characteristics of the visual cortex.

More plausible explanations for the evolution of a visual-aura-like wave (supposedly the scotoma) are provided by the third model, that of Dahlem and Muller, but controversy still exists upon these explanations, as we discussed previously. Topographic maps are again not taken into account in this model.

Finally, the model of Dahlem, Engelmann, Lowel and Muller is of much importance. It captures characteristics of the fortification shape by utilizing information from topographic maps interpreted as a CSD-like simulated wave propagates on them. Obviously, the last two models could be combined.
after some tuning in order to provide a unified model of both the scotoma and the fortification pattern.

As the brain imaging techniques are not satisfyingly adequate for providing satisfyingly low-level details in such cases, one of the basic aims of such models should be to reach deeper neurological predictions and explanations. Given that the patients’ descriptions of their auras cannot be extremely precise and that it is possible that the expression of the phenomenon itself depends on several factors (age, sex, severity and frequency of the migraines), the modeling research should mainly focus on a top-down rather than on a bottom-up approach in the future.

The above approaches put much more emphasis and effort in recreating the visual aura phenomenon. Different background neurological information is utilized but a holistic model that embodies all the underlying neurological information has not been proposed yet, even if this information is to be utilized in an appropriately abstract manner.

In our opinion, a model that would consider the systematic effects of the potassium dynamics, the topographic maps, the structure of the visual cortex and possibly other neurological findings, like the role of certain neurotransmitters, and that would be built on a neural network structural basis, would be more useful for providing more holistic insights both into the migraine aura and the CSD phenomenon, while it would still have the potential to aid in deeper predictions for other migraine and cortical mechanisms.

An alternative that could possibly be incorporated in a model in order to achieve the simulation of the propagation failure of the aura could be a depletion mechanism for potassium and/or glutamate concentration. If something like that is biologically plausible and feasible from a modeling point of view, it could replace the kinematical and wave-theoretical modeling aspects.

Another hypothesis that could be tested for the same reasons could be whether the restoration of the habituation mechanism could stop CSD. If this happened shortly after the initiation of CSD, habituation could possibly contribute to the stopping of CSD some time after its initiation (a short description for habituation is provided in the first footnote of the introductory section). Habituation is supposed to be dysfunctional in migraineurs when not under attack, but surprisingly it has been found to function normally during attacks.

An outstanding question is why the propagation direction of the visual aura seems to almost always be from the center to the visual field towards its periphery. The current models do not prevent a reverse spread [2]. Therefore more focus in terms of modeling should be placed there. It could be that CSD initiates from a neighboring to V1 area (area V3A has been denoted at some experiments) before migrating to the primary visual area. The initiation of CSD might be crucial to its further evolution, so it is possible that the incorporation of such an initiation phase could be useful or even necessary for the models.

A further issue to be considered is how the CSD phase affects and sets the ground for the next phases of the migraine, that is, those taking place during the main attack. Still major sensory and cognitive deficits appear during that time. As an attack could last over 24 hours, certain mechanisms that preserve (and indeed up to a point gradually strengthen) such abnormal cortical activities should exist and might share commonalities with CSD.

One more question is whether another mechanism precedes CSD and initiates it. Up to now, this initiation has been attributed to the combination of the cortical hyper-excitability of the migraineurs and external stimuli. Although there is no experimental evidence for a phase like that, certain facts might point to it: for example the transition from increased external stimulation to the increase in potassium concentration is not well explained yet. It could be attributed to decreased intracortical inhibition or other malfunctions. This alone could support the periodicity of migraine attacks due to an accumulative effect, but does not explain very well the rapid initiation of a migraine attack under heavy exposure to certain migraine triggers.
Moreover, an outstanding question that to the best of our knowledge has not been set yet is how the CSD phenomenon and its two parts of extreme activity and deep activity depression could be connected with long-term synaptic plasticity. This question is extremely crucial for chronic patients with frequent attacks. It would be important to know if migraines cause any long-term problems in cognitive functions and if the cortical areas become more resistant or more susceptible to CSD as the years go passing by.

It has to be noted here that there exists open software for simulating topographic maps like Topographica that could be extended in order to recreate the visual aura phenomenon: a propagating CSD-like wave has to be simulated so as to propagate on a V1 topographic maps and through the method of population vector response estimation and reverse retinotopic mapping (as described in [6]) the resulting visual aura could hopefully be easily obtained.

Hopefully, the combined study of CSD and the migraine aura could provide us with enough knowledge so that research could proceed to “silent” CSD mechanisms in other cortical areas that might occur in migraines without aura. Before getting there, all the available information concerning the phenomenon and the primary visual cortex should be exploited. The well-studied nature of the latter and the “tangible” information from the aura form together an excellent chance to dive deeper into the cortical structure and functions.

5. Conclusion

Following from the above discussion, it can be seen that many important questions concerning this research field still remain outstanding. As far as modeling is concerned, more holistic and elaborated models that incorporate suitable neurological information would be useful in proceeding in deeper cortical mechanisms. It is hoped that this research can provide significant insights concerning the Cortical Spreading Depression phenomenon, the (visual) migraine aura, the migraine disease itself and possibly other related diseases, like epilepsy [1].

Apart from the discovery of more effective medical treatments, the study and modeling of the above topics could eventually shed a significant amount of light to the overall healthy brain function.

Bibliography