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A Computational Model of Acute and Delayed Tissue Damage Resulting From Ischemic Stroke

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Stroke is the 3rd leading cause of pre-mature death in the world according to the World Health Organisation, afflicting approximately 500,000 people per annum in the United States alone [3]. Ischemic stroke, either from an embolism or thrombosis accounts for 85% of stroke incidence. Although stroke research has not found a "cure," great progress has been made from experimental models of stroke[4,6]. The primary results from experimental models of ischemic stroke are: i) the glutamate excitotoxicity hypothesis and the ii) cortical spreading hypothesis [4]. The glutamate excitotoxicity hypothesis postulates that tissue damage causes the release of lethal doses of glutamate into the extra-cellular space which in turn diffuses locally causing excitotoxic neuronal activation. This process continues until glutamate levels can be buffered below toxic levels. In the cortical spreading depression (CSD) hypothesis, tissue damage causes a release of potassium into the ECS, which induces metabolic overload from ionic disequilibria and/or neuronal hyperexcitability. Experiments, which have prevented these events from occurring (applying the glutamate antagonists MK801), result in decreased tissue damage of the order of 30% below that of controls [4,6]. Although these results are promising, clinical trials have not yielded the same level of tissue protection. Currently, there are no clinical trials that have provided clinical support of experimental findings with regards to tissue reduction in ischemic stroke. The amount of money required to bring a drug through clinical trials can be prohibitive – therefore any methodology, which might reduce the cost of therapeutic drug design, would be advantageous. It is hoped that computational models of diseases such as stroke might provide a fast, efficient, and cost-effective method which to evaluate mechanisms of action to be investigated. A critical factor in this area of research entails the extent to which biological information can be incorporated into these models. This in turn depends on the representational capacity of the model and the computational platform upon which the model executes. It is hoped that Moore's Law of computational capacity doubling time will persist into the near future. In this paper, an extension of a biologically realistic model of ischemic stroke is presented outlining current adaptations and future plans.

In this paper, an extension of a biologically realistic computational model of acute ischemic stroke is introduced (see [8] for details on the base model). The model incorporates many of the relevant biochemical/neurophysiological changes that have been implicated in tissue damage from clinical and experimental models of ischemic stroke. These changes can be broadly classified into the following categories: i) ionic imbalances (Na,K,Cl and Ca), ii) metabolic factors such as ATP levels and cerebral blood flow (CBF), iii) neurotransmitters such as glutamate, and iv) mediators of tissue damage such as free radicals, apoptosis, and necrosis. The model yields results that are consistent with much of the experimental literature, such as the linear relationship between the number of CSD waves and tissue damage, the role of glutamate excito-toxicity and tissue damage, CSD

waves do not cause tissue damage in normally perfused tissue, to name a few. The model thus accounts for *acute* tissue damage reasonably well. Yet, in the clinical literature, a phenomenon termed *stroke-in-progression* has been reported to occur in up to 40% of stroke cases [4]. Although there is no universal definition of this phenomenon, a recurrent observation is a secondary phase of tissue damage following a quiescent period. Several hypotheses have been proposed: reperfusion injury subsequent to re-canalisation and more recently apoptosis have been proposed to account for this phenomenon [2 for a review]. The present and future implementation of the model discussed in this paper incorporates tissue damage that occurs with a similar temporal profile to stroke-in-progression, and focuses on apoptosis as the mediator of this phenomenon. What is unique about this proposal – resulting from the computer simulation of stroke, is the hypothesis that apoptosis may produce a secondary bout of CSD waves. It is argued that if CSD waves can cause damage in the acute phase, then it may be feasible to expect that CSD mediated damage could occur in a delayed fashion.

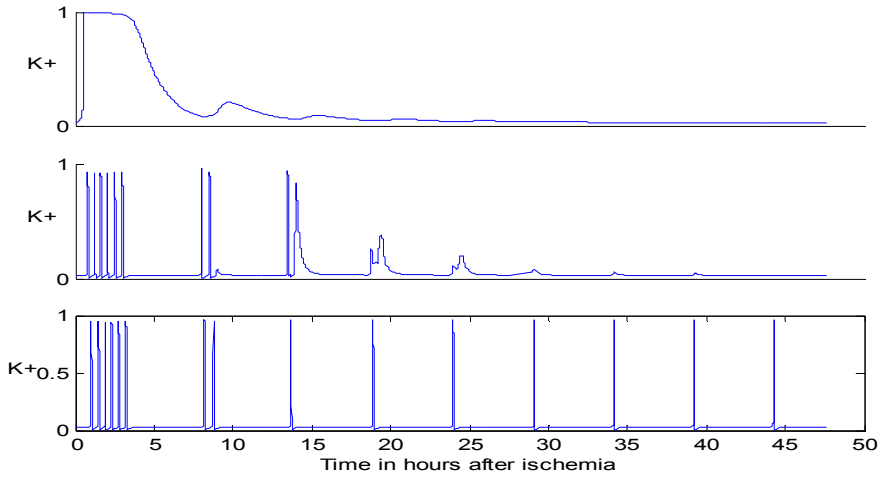
Evidence from several models of apoptosis consistently reveal a phenomenon termed the apoptotic volume decrease (AVD), which is associated with a large potassium efflux – upwards of 70% of intracellular potassium effuses from the cytoplasm as a prerequisite for apoptosis [1,5]. An interesting question is: where does this potassium go – what pathways are used in AVD? Some have suggested specific potassium channels that are activated in Kv2.1-encoded potassium channels [7]. It is also possible that gap junction are required. Whatever the pathway, it is clear that a substantial amount of potassium effuses from the cytoplasm – the hypothesis presented here is: is there enough potassium effusion to generate CSD waves. In addition to a positive answer to this question – the timing of apoptosis mediated CSD waves is critical as well. This hypothesis would predict a secondary set of CSD waves occurring on the time scale of apoptosis – which has been reported in various tissue types to be anywhere from 3-12 or more hours after stimulus presentation – in this case, the original ischemic insult. Corroborating evidence for a delayed secondary bout of CSD waves following transient MCA occlusion in the awake rat has been recently published [3].

It is quite clear that apoptosis – being a form of cell death will cause tissue damage – could it also cause tissue damage through the formation of CSD waves to the same extent that occurs during the acute phase? Numerous studies have provided evidence that pre-ischemic conditioning – such as a short (10 minute) exposure to ischemia 24-72 hours prior to severe ischemia is neuroprotective: the final damage is reduced by as much as 30% compared to controls with no pre-ischemic conditioning [9]. We used this computational model of stroke to examine this question and found that damage normalised per CSD wave is 40% less in the delayed phase compared to the acute phase. In order to investigate this result more appropriately, one must normalise the damage based on the metabolic status of the tissue – it is well known that CSD waves do not cause damage in healthy tissue. Since delayed CSD waves may spread from their site of origin across tissue that is better perfused and therefore able to better withstand their debilitating affects than that occurring in the acute phase, one must take the 'resistance' level into account. These are tasks that are vitally important in characterising events subsequent to stroke, but are very difficult to do experimentally. This is where the power of computational modelling can enhance experimental or clinical work.

The computer simulation consists of a hexagonally tessellated 2D representation of cortical tissue. Within each cellular element (corresponding to a cortical column and represents an area of approximately 100x100mm of cortex), state variables are embedded

and their temporal and spatial evolution is allowed to occur in a biologically realistic manner, using a Forward Euler update algorithm. As mentioned previously, there are 5 major classes of state variables, selected from literature search and our own work on experimental stroke. The state variables are recorded at fixed spatial locations within the simulation of the cortex. The simulated cortex contains 3 distinct regions, distinguished by their supply: a central core region with 0 ml/100gm/min CBF, a penumbra, a region of reduced CBF (graded linearly according to the fractional distance from the edge of the ischemic core) that surrounds the ischemic core surrounded by normal tissue. Three probes – one in each tissue compartment record the values of all state variables over time. In Figure I below, the value of extracellular potassium (K^+) is displayed as it varies over time at the three probe sites.

Figure I: recording of extracellular potassium levels at the ischemic core, penumbra, and surrounding normal tissue (top to bottom).



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