Drug Discovery Today: Disease Models
Vol. xxx, No. xx 2017

Computer modeling of ischemic stroke

Adam J.H. Newton[1], William W. Lytton[1,2,3,*]

[1]Department of Physiology & Pharmacology, SUNY Downstate, Brooklyn, NY, United States
[2]Department of Neurology, SUNY Downstate, Brooklyn, NY, United States
[3]Department of Neurology, Kings County Hospital Center, Brooklyn, NY, United States

The occlusion of a blood vessel in the brain causes an ischemic stroke. Current treatment relies on restoration of blood flow within 3 hours. Substantial research has focused on neuroprotection to spare compromised neural tissue and extend the treatment time window. Despite success with animal models and extensive associated clinical testing, there are still no therapies of this kind. Ischemic stroke is fundamentally a multiscale phenomenon where a cascade of changes triggered by loss of blood flow involve processes at spatial scales from molecular to centimeters with damage occurring in milliseconds to days and recovery into years. Multiscale computational modeling is a technique to assist understanding of the many agents involved in these multitudinous interacting pathways to provide clues for *in silico* development of multi-target polypharmacy drug cocktails.

Section editors:
William Lytton – Department of Physiology and Pharmacology, SUNY Downstate Medical Center, Brooklyn, New York, USA and Department of Neurology, Kings County Hospital Center, Brooklyn, New York, USA.
Sam Neymotin – Department of Neuroscience at Brown University, Providence, Rhode Island, USA.

Introduction

Stroke is a major cause of death or disability, the 5th leading cause of death in the US with prevalence of ~2.6% of the adult population [1]. Around 85% of strokes are ischemic [2]. Neuroprotective strategies would target the myriad destructive processes that occur following a stroke, including spreading depression, excitotoxicity, cytotoxic edema, accumulation of free radicals, etc., in order to extend the treatment time window and reduce the volume of damaged brain tissue. Here we review current computational modeling efforts and consider their usefulness as a bridge for drug discovery which will help close the current gap between animal models and clinical trials.

Background

The many causes and types of stroke require vastly different approaches to prevention and treatment, and vastly different approaches to the type of multiscale modeling (computer simulation) that is used. For example, prevention of hemorrhagic stroke due to a blood vessel aneurysm must be understood in terms of laminar or turbulent blood flow under pressure and the various layers of the blood vessel that must fail, to give rise to this type of stroke; treatment would then be surgical prophylaxis for aneurysms deemed prone to bursting. Modeling ischemic stroke could also focus on the vascular system but would include pathophysiology of platelets, clotting cascades in the blood, to determine the likelihood of thrombosis formation. Such a kind of modeling approaches are particularly valuable to further understanding of the current standard of care through reperfusion. By contrast, cardiogenic stroke syndromes and preventive therapy would best be understood by modeling the left atrium of the heart. In this review, we will not look at either of these stroke types

*Corresponding author: W.W. Lytton (bill.lytton@downstate.edu)

 http://dx.doi.org/10.1016/j.ddmod.2017.01.001

Please cite this article in press as: Newton AJH, Lytton WW. Computer modeling of ischemic stroke, Drug Discov Today: Dis Model (2017), http://dx.doi.org/10.1016/j.ddmod.2017.01.001

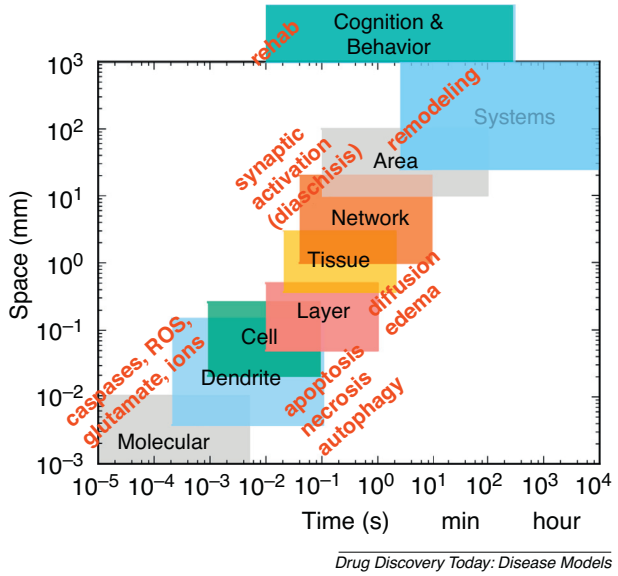

Figure 1. Many scales of brain organization inform our understanding of stroke with different responses to stroke ranging in time from milliseconds to years. In this review we focus on the changes that occur at molecular, cell, tissue and network levels, noting the interplay of neuronal network synaptic interactions with bulk tissue interactions.

but will instead focus on the effects of ischemia on brain tissue. Of course, even the brain sans blood and blood vessels is itself a complex subject with many scales of interactions from molecular to tissue and network levels (Fig. 1). Within the brain, study of stroke includes additional topics of brain response, relevant to neurorehabilitation and recovery, as we have discussed elsewhere [3,4].

Damage to tissue in ischemic stroke is divided into three regions: (1) an infarct core where cells suffer irreparable damage and death, (2) a penumbra where cells may recover with reperfusion or with the assistance of neuroprotective therapy, (3) a further region of edema (benign oligemia) where spontaneous recovery is expected (Fig. 2).

The penumbra, vulnerable but salvageable, is the target of *neuroprotection strategies* (Fig. 2c). Unfortunately, despite thousands of experimental studies on neuroprotection, and hundreds of clinical trials, there are no approved neuroprotective drugs [5]. Agents that have been tried include Ca^{2+} antagonists [6], NMDA receptor antagonists [7] and free radical scavengers [8]. Neuroprotective agents that achieve substantial tissue sparing in animal models have resulted in high profile clinical-trial failures. The *clinical translation* problems result both from discrepancies between the experimental and clinical treatments and from underlying biological differences between test animals and humans.

Multiscale mechanistic computer simulation has the potential to bridge the gap between animal models of ischemic stroke and patient outcomes and to facilitate development of drug cocktails by improving our understanding of the many agents and processes involved in cell death. Computer modeling will elucidate the many nonlinearities in time (early, mid, late death) and in space (multiple cores and multiple penumbra). The volume of penumbra decays exponentials as cells die and the core expands. It has been estimated that ~2 million neurons die every minute following a stroke [9]. However, the many causes of cell damage and death are produced by feedback loops which are highly nonlinear (Fig. 3), and this average value of 2 million is expected to be unevenly distributed in both time and space.

Multiscale computational modeling in neuroscience is based on biophysically detailed models of neuronal circuits with pharmacologically relevant parameters [10], with spatial scales from brain regions to a single synapse and time-scales spanning single action-potentials to hours or even days. Such detailed models can identify key additional data required, provided quantitative predictions and hypothesis testing [11] and potentially provide an *in silico* platform for drug discovery [12]. Computational neuroscience has traditionally built models focused on electrophysiology, synaptic signaling and corresponding network activity [13]. However, multiscale modeling for ischemic stroke must involve not only neuronal

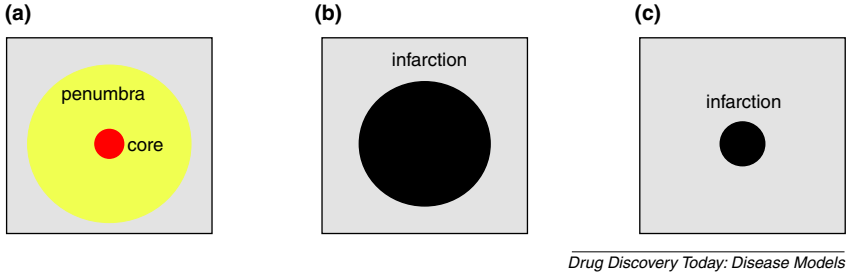

Figure 2. The goal of neuroprotection following an ischemic stroke is to reduce the tissue damage and subsequent functional impairment. There are numerous potential targets for neuroprotective therapies, across multiple temporal and spatial scales. **(a)** Simple depiction of the core and penumbra following an ischemic stroke. **(b)** A large infarct as many of the cells in the penumbra die. **(c)** A goal of neuroprotection, preserving the penumbra.

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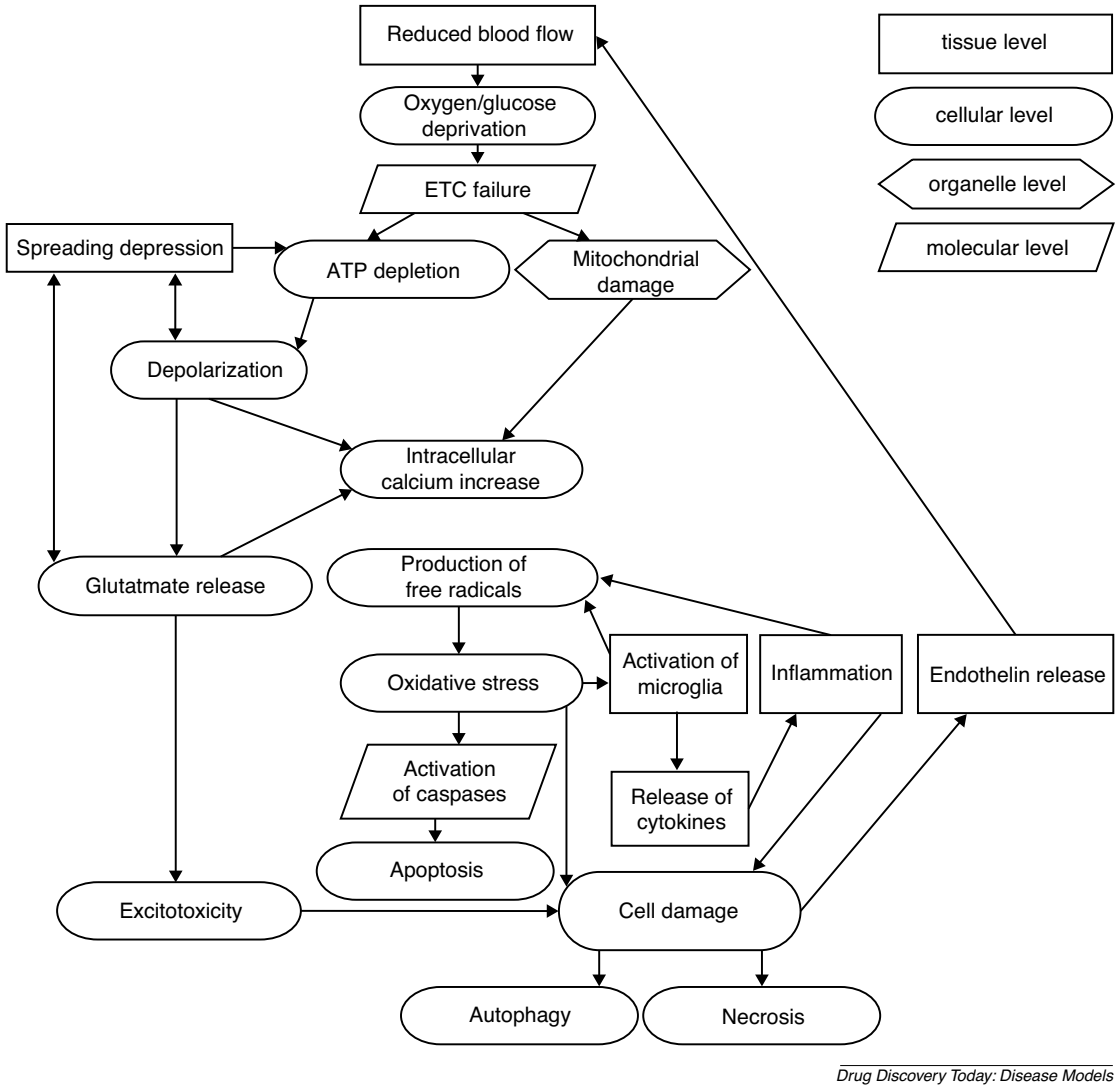

Figure 3. Schematic representation of some of the processes and pathways involved in ischemic stroke that result in cell damage or death. Multiple scales are denoted by different shapes. Several positive feedback loops amplify damaging signals and provide many potential targets for neuroprotection. ETC, electron transport chain.

activity, but also intracellular and extracellular molecular dynamics.

Cellular scale modeling

Modeling single cells and the subcellular events that follow ischemic stroke is essential to understand the intracellular ischemic cascade, a series of biochemical reactions following ischemic insult that lead to cell damage or death. The cascade occurs over multiple time-scales, with the initial rapid changes in cell metabolism and ionic concentrations trigging several agents that may ultimately lead to cell death days or even weeks later.

There are three main modes of cell death: (1) apoptosis – programmed cell death; (2) autophagocytosis – the cell devours itself; (3) necrosis – rapid death where the products of cell death leak out to extracellular space (ECS).

There are also intermediate forms such as necroptosis. Although dead cells will be broken-down by microglia, necrotic cells are likely to cause further damage to the surrounding tissue before they are removed. The primary cause of cell death in ischemia is loss of glucose and oxygen, which reduces or prevents oxidative phosphorylation, the metabolic pathway that forms ATP. This triggers early ionic changes in the cell which in turn activate several damaging processes or perpetrators [14]. Cell death can occur within hours of ischemic stroke or weeks later. The mode and timing of cell death may not be determined by one particular perpetrator, but result from the complex interactions among multiple pathways.

A typical storm of early ischemic changes in the cell includes a decrease in pH, the production and release of free radicals, failure of the Na^+-K^+ pump due to lack of ATP,

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membrane depolarisation and subsequent influx of Ca^{2+} via voltage-gated calcium channels. Depolarization leads to a rise in extracellular K^+, which may cause other neurons to depolarize in a phenomenon known as spreading depression. Influx of Ca^{2+} is augmented by calcium induced calcium release from endoplasmic reticulum. Elevated intracellular Ca^{2+} causes vesicles release, and glutamate that spills out into the ECS can extrasynaptically excite surrounding neurons. Both synaptic process and extracellular glutamate contribute to *excitotoxicity*, a neuronal damage through excessive stimulation [15]. Excitoxicity is particularly potent in the low nutrient environment of the penumbra since impaired cells cannot keep up with the increased metabolic demands. Cytotoxic edema (accumulation of water inside cells) results from osmotic movement of water into cells [16]. Astrocytic swelling reduces the volume fraction of ECS, causing further increase in concentration of damaging agents [17]. The rapid changes trigger several perpetrators, agents believed to be responsible for the functional and structural changes that lead to cell death, such as calpain (part of a family of calcium dependent enzymes that break down the cytoskeleton and may damage ion channels), and phospholipase activation that breaks down cell membranes [14]. Free radicals are a key perpetrator and include ROS and reactive nitrogen species (RNS). ROS are produced in mitochondria when the electron transport chain fails and are removed by scavenging enzymes. Oxidative stress occurs when the production of ROS exceeds the cell's ability to remove them. Nitrogen oxide (NO) is a neurotransmitter and neuromodulator; though it is necessary to maintain vascular tone and cell homeostasis, it is rapidly cleared with a half-life of a few seconds. Production of NO by nitric oxide synthase (NOS) increases ~20× in. ischemic stroke. Toxicity then occurs directly or via the formation of peroxynitrite, a RNS.

There are many models that focus on cell damage and death under a variety of pathological conditions, which are relevant to the understanding and model development for ischemic stroke. For example, in a model of mitochondria of a pancreatic β-cell, suspension of the electron transport chain (as would occur in ischemic conditions) leads to the failure of proton pump and subsequent high mitochondria membrane potential, resulting in an increase in proton leak and a corresponding increase in ROS [18]. Models of oscillations between the protein Mdm2 and gene p53 showed that Ca^{2+} induced increases NOS shift the systems from sustained oscillation to an oscillation death regime [19], emphasising the importance of considering noise in the system because of the low copy number. Detailed biophysical models of apoptosis, particularly focus on caspase, the principle signalling pathway for cell suicide. Caspase is activated by binding of surface receptors or in response to oxidative stress. Modeling has to identify factors that lead to the heterogeneity of cell fates, protein interactions that can promote or suppress apoptosis and have the potential for *in silico* drug development [20–23]. Intracellular Ca^{2+} plays a vital role in neuronal signalling and biophysiology, so it has been extensively modeled in both physiological [24] and pathological conditions [25], and it is also a principle agent in the ischemic cascade (Fig. 3), penumbra responsible for much of the subsequent toxicity. Such models are valuable for future development of multiscale models of ischemic stroke.

Tissue scale modeling

Spreading depression is a wave of depolarization that propagates through tissue at 2.5–7 mm/min and can last at a particular location for ~1 min. Spreading depression results from several causes but one that is best explored is due to the leak of K^+ from cells with spread through ECS and subsequent depolarization with further release from affected cells, with extracellular K^+ levels exceeding K^+ a threshold ~27 mM that is modulated by NO [26]. Spreading depression is seen not only in ischemic stroke, but also in migraine and epilepsy. In the latter disorders, there is sufficient energy so that the depolarized cells will repolarize once the excessive extracellular K^+ is cleared by astrocytes. In ischemic spreading depression, this clearance and repolarization will fail. Phenomenological models have attempted to capture the key events while abstracting away from the biophysical details. One model for spreading depression used functions to represent blood flow, energy (available and required), cellular damage and ability to repair, with the mode of cell death determined by simple thresholds. The model showed a correlation between the temporal frequency of spreading depression waves and the rate of expansion of the core. Repeated spreading depression waves increased core size by ~30% [27]. Mathematical modeling indicated an essential role for the Na^+-K^+ pump, which fails in ischemic causing K^+ to leak into the ECS [28] and cellular swelling, which greatly reduces the volume of the ECS while increasing the tortuosity [29].

At the tissue scale it is necessary to consider the extracellular changes in the ischemic cascade. Concentration changes of ions and molecular signals of cell damage diffuse thought the ECS at various rates influencing a large volume of tissue. Within minutes of ischemic stroke the cells at the core are fatally damaged and undergo necrosis, cells in the penumbra will also perish if not protected until blood supply is restored. Measurements from diffusion weighted MRI (DWI) indicate a rapid growth in the core over the first 3 hours after stroke [30]. Inflammation is triggered following ischemic stroke. At early stages, inflammation is harmful, increasing the concentration of free radicals and intracranial pressure. Later, inflammation may be beneficial as it clears dead cells to allow rewiring. Two key cell classes for inflammation in the brain are microglia and leukocytes. Microglia are rapidly activated following an ischemic stroke and will eliminate dead cells via

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phagocytosis. In doing so, they release free radicals, NO and pro-inflammatory cytokines. Cytokines attract leukocytes from the blood. Within hours of the stroke, neutrophils enter which can be harmful as they enzymatically degrade cells. After around 24 hours, macrophages enter and perform further phagocytosis, clearing dead tissue from the infarct core. A detailed mathematical model was developed that considered the densities of these cells in different tissue states – healthy, necrotic, apoptotic and undergoing apoptosis [22]. That model revealed a nonlinear relationship between initial core volume and the ultimate size of the infarction. These data could then be used to predict the efficacy of anti-inflammatory therapy.

Ischemia triggers yet another positive feedback loop as vasoconstrictor substances such as endothelin are released and further reduces blood flow. Some models have incorporated the blood flow implicitly in terms of availably energy and oxygen [27,28]. More detailed multiscale models of cerebral blood flow have also been developed [11]. Some of these can use patient-specific computational fluid dynamics to determine regions at risk for thrombosis development [31] and could identify patient-specific drug responses [32].

Multiscale modeling for neuroprotective drug discovery

Targeted nanotherapy will provide the ability to target specific brain regions or specific cell types. Synthetic polymers have been developed for improved drug delivery. Stimuli-responsive polymers can respond in a given way in accordance with the change of cell shape, permeability or electrical properties, or in response to temperature, pH or electrical fields [33]. Given the acidification that occurs in ischemic stoke, such stimulus-response polymers have the potential to deliver therapeutic agents to particular parts of the penumbra where efficacy is predicted by detailed modeling of the pH changes expected under certain circumstances [34]. As noted above, many processes of cell death and tissue disruption associated with ischemia are highly nonlinear in both time and space. For this reason, we propose that drug delivery might best be targeted in space according to specific criteria. Although targeting drug delivery at particular delivery times may also be valuable, we note that the many processes of penumbra evolution will be distinct across the affected region so that different regions will be at different stages of evolution in the peri-infarct period. We propose this type of drug discovery as another form of medical *precision*. *Precision medicine* refers to the selection of particular groups of patients according to various grouping which often depend on the patients' genomes. *Precision drug targeting*, already used for tumors, refers to the precise targeting of particular sets of cells according to these cells' shared attributes over the course of disease progression.

Spreading depression causes cells in the penumbra to expend energy they can ill afford to waste, increasing their vulnerability to cell death. Preventing spreading depression is of interest not only to treatment of ischemic stroke, but also for migraine and epilepsy. This suggests that antimigraine drugs, which prevent spreading depression, could be tried in ischemic stroke. However, differences in the state of the tissue can substantially alter the efficacy of such a treatment so here again targeting therapy to particular states of the penumbra defined by location relative to the core or by the time after the stroke initiation could be valuable. For example, NMDA receptor antagonists are effective at limiting the waves of spreading depression in normal tissue. However, excessive extracellular K^+ is sufficient to cause spreading depression with little influence from synaptic transmission under pathological conditions [35]. Here again, precise targeting of an NMDA antagonist that depends on the details of the local tissue environment may be valuable. Computational modeling will be used to inform the relative contribution of the different causes of spreading depression, and to identify and modify the relevant parameters to provide an estimate of efficacy at particular times following the stroke, perhaps in combination with other therapeutic agents.

Many other proposed neuroprotective strategies could be assessed by modeling [36]. Examples include (1) Ca^{2+} channel antagonists [37]. Multiscale modeling could here evaluate the relative efficacy in inhibiting the different routes by which excessive Ca^{2+} can enter the cell, distinguishing pre- and postsynaptic processes. These would include presynaptic voltage-gated channels and NMDAR which would increase glutamate release, calcium-induced calcium release from organelles, stretch-activated calcium channels that might respond to the stretch associated with edema, and acid-sensing ion channel. Other factors that could be considered would be the effects of channel antagonists on blood pressure reduction. (2) Inhibiting the aquaporin-4 (AQP4) water channels [38]. Non-steroid anti-inflammatory drugs (NSAIDs) have a large number of effects which are not restricted to inflammatory agents but include effects on the aquaporin channels. This wide variety of NSAID effects have been the subject of modeling [39], which could now be extended to the special considerations encountered in ischemic brain tissue. For example, the effects on aquaporins could reduce cytotoxic edema and thereby reduce local extracellular concentrations of toxic molecules and decrease tortuosity so as to increase clearance of these molecules to sites beyond the penumbra. NSAIDs also inhibit some types of Ca^{2+} channels and could reduce in Ca^{2+} influx [39]. NSAIDs reduce prostoglandins which play a variety of roles mediated by at least 10 receptor subtypes. (3) Inhibiting leukocytes interaction with endothelial cells [40]. Inflammation is a response to injury which causes further injury, particularly in the skull-case which provides no room for expansion. General cell

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density models for inflammation can distinguish between microglial and leukocyte inflammation to begin to calculate how inhibition of aggregation could affect infarct size in each case [22]. However, these models lack key features that are peculiar to the brain and to ischemic stroke, such as the effects of production and diffusion of ROS, which activate microglia and can be produced by them. The disruption of endothelial cells and of the blood brain barrier in ischemic stroke leads to particular patterns of accumulation of leukocytes such as polymorphonuclear cells. Other components of the neurovascular-unit will also contribute to immune responses following ischemic stroke.

Conclusion

Individually, several of the existing ischemic stroke models have the potential for *in silico* experiments and drug development focusing on a single aspect of stoke pathology, for example, thrombosis formation [31] or inflammation [22]. Future developments should seek to combine the multiple features together with sufficient biophysical detail to facilitate the search for multi-target drug cocktails.

Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgement

This work was supported by National Institute of Mental Health research grant R01 MH086638.

References

[1] NCHS. Summary health statistics: national health interview survey; 2014, http://www.cdc.gov/nchs/nhis/SHS/tables.htm.
[2] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Executive summary: heart disease and stroke statistics – 2016 update: a report from the American Heart Association. Circulation 2016; 133(4):447.
[3] Lytton WW, Williams ST, Sober SJ. Unmasking unmasked: neural dynamics following stroke. Prog Brain Res 1999;121:203–18.
[4] Lytton WW, Stark JM, Yamasaki DS, Sober SJ. Computer models of stroke recovery: implications for neurorehabilitation. Neuroscientist 1999;5:100–11.
[5] Ginsberg MD. Neuroprotection for ischemic stroke: past, present and future. Neuropharmacology 2008;55(3):363–89.
[6] Horn J, Limburg M. Calcium antagonists for ischemic stroke a systematic review. Stroke 2001;32(2):570–6.
[7] Ikonomidou C, Turski L. Why did NMDA receptor antagonists fail clinical trials for stroke and traumatic brain injury? Lancet Neurol 2002;1(6): 383–6.
[8] De Keyser J, Sulter G, Luiten PG. Clinical trials with neuroprotective drugs in acute ischaemic stroke: are we doing the right thing? Trends Neurosci 1999;22(12):535–40.
[9] Saver JL. Time is brain – quantified. Stroke 2006;37(1):263–6.
[10] Geerts H, Roberts P, Spiros A, Carr R. Multi-scale modeling of drug action in the nervous system. In: Systems pharmacology and pharmacodynamics. Springer; 2016. p. 305–24.
[11] Xu Z, Chen N, Kamocka MM, Rosen ED, Alber M. A multiscale model of thrombus development. J R Soc Interface 2008;5(24):705–22.
[12] Neymotin SA, Dura-Bernal S, Lakatos P, Sanger TD, Lytton W. Multitarget multiscale simulation for pharmacological treatment of dystonia in motor cortex. Front Pharmacol 2016;7:157.
[13] De Schutter E. Why are computational neuroscience and systems biology so separate. PLoS Comput Biol 2008;4:e1000078.
[14] Lipton P. Ischemic cell death in brain neurons. Physiol Rev 1999; 79(4):1431–568.
[15] Hardingham GE, Bading H. Synaptic versus extrasynaptic NMDA receptor signalling: implications for neurodegenerative disorders. Nat Rev Neurosci 2010;11(10):682–96.
[16] Chen Y, Swanson RA. Astrocytes and brain injury. J Cereb Blood Flow Metab 2003;23(2):137–49.
[17] Hrabětová S, Hrabe J, Nicholson C. Dead-space microdomains hinder extracellular diffusion in rat neocortex during ischemia. J Neurosci 2003;23(23):8351–9.
[18] Heuett WJ, Periwal V. Autoregulation of free radicals via uncoupling protein control in pancreatic β-cell mitochondria. Biophys J 2010; 98(2):207–17.
[19] Alam MJ, Devi GR, Ishrat R, Subhash M, Agarwal RK, Singh B, et al. Switching p53 states by calcium: dynamics and interaction of stress systems. Mol Biosyst 2013;9(3):508–21.
[20] Mai Z, Liu H. Boolean network-based analysis of the apoptosis network: irreversible apoptosis and stable surviving. J Theor Biol 2009; 259(August (4)):760–9.
[21] Fussenegger M, Bailey JE, Varner J. A mathematical model of caspase function in apoptosis. Nat Biotechnol 2000;18(July (7)):768–74.
[22] Di Russo C, Lagaert J-B, Chapuisat G, Dronne M-A. A mathematical model of inflammation during ischemic stroke. In: ESAIM: Proceedings, vol. 30. EDP Sciences; 2010. p. 15–33.
[23] Xia X, Owen MS, Lee REC, Gaudet S. Cell-to-cell variability in cell death: can systems biology help us make sense of it? Cell Death Dis 2014;5(5): e1261.
[24] De Schutter E. Computational modeling methods for neuroscientists. The MIT Press; 2009.
[25] Diekman CO, Fall CP, Lechleiter JD, Terman D. Modeling the neuroprotective role of enhanced astrocyte mitochondrial metabolism during stroke. Biophys J 2013;104(8):1752–63.
[26] Petzold GC, Haack S, und Halbach OvB, Priller J, Lehmann T-N, Heinemann U, et al. Nitric oxide modulates spreading depolarization threshold in the human and rodent cortex. Stroke 2008;39(4): 1292–9.
[27] Chapuisat G, Dronne M-A, Grenier E, Hommel M, Gilquin H, Boissel J-P. A global phenomenological model of ischemic stroke with stress on spreading depressions. Prog Biophys Mol Biol 2008;97(1):4–27.
[28] Wei Y, Ullah G, Schiff SJ. Unification of neuronal spikes, seizures, and spreading depression. J Neurosci 2014;34(35):11733–43.
[29] Ullah G, Wei Y, Dahlem MA, Wechselberger M, Schiff SJ. The role of cell volume in the dynamics of seizure, spreading depression, and anoxic depolarization. PLoS Comput Biol 2015;11(8):e1004414.
[30] Tymianski M. Novel approaches to neuroprotection trials in acute ischemic stroke. Stroke 2013;44(10):2942–50.
[31] Rayz VL, Boussel L, Lawton MT, Acevedo-Bolton G, Ge L, Young WL, et al. Numerical modeling of the flow in intracranial aneurysms: prediction of regions prone to thrombus formation. Ann Biomed Eng 2008;36 (11):1793–804.
[32] Flamm MH, Colace TV, Chatterjee MS, Jing H, Zhou S, Jaeger D, et al. Multiscale prediction of patient-specific platelet function under flow. Blood 2012;120(1):190–8.
[33] Schmaljohann D. Thermo- and pH-responsive polymers in drug delivery. Adv Drug Deliv Rev 2006;58(15):1655–70.
[34] Orlowski P, Chappell M, Park CS, Grau V, Payne S. Modelling of pH dynamics in brain cells after stroke. Interface Focus 2011. rsfs20100025.
[35] Lauritzen M, Dreier JP, Fabricius M, Hartings JA, Graf R, Strong AJ. Clinical relevance of cortical spreading depression in neurological disorders: migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. J Cereb Blood Flow Metab 2011;31(1): 17–35.

Please cite this article in press as: Newton AJH, Lytton WW. Computer modeling of ischemic stroke, Drug Discov Today: Dis Model (2017), http://dx.doi.org/10.1016/j.ddmod.2017.01.001

[36] Chamorro Á, Dirnagl U, Urra X, Planas AM. Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. Lancet Neurol 2016;15(8):869–81.
[37] Zhang J, Yang J, Zhang C, Jiang X, Zhou H, Liu M. Calcium antagonists for acute ischemic stroke. Cochrane Libr 2012.
[38] Bhattacharya P, Pandey AK, Paul S, Patnaik R, Yavagal DR. Aquaporin-4 inhibition mediates piroxicam-induced neuroprotection against focal cerebral ischemia/reperfusion injury in rodents. PLoS ONE 2013;8(9):e73481.
[39] Dorofeeva NA, Barygin OI, Staruschenko A, Bolshakov KV, Magazanik LG. Mechanisms of non-steroid anti-inflammatory drugs action on ASICs expressed in hippocampal interneurons. J Neurochem 2008;106(1):429–41.
[40] Gregory J, Zoppo D. Acute anti-inflammatory approaches to ischemic stroke. Ann New York Acad Sci 2010;1207(1):143–8.

Please cite this article in press as: Newton AJH, Lytton WW. Computer modeling of ischemic stroke, Drug Discov Today: Dis Model (2017), http://dx.doi.org/10.1016/j.ddmod.2017.01.001