Journal of Computational Systems Biology
Volume 4 | Issue 1
ISSN: 2455-7625
Research Article
Open Access

Computer Modeling of Convective Mass Transfer of Glucose, Oxygen and Carbon Dioxide in the Neurovascular Unit

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Citation: Titovets E (2019) Computer Modeling of Convective Mass Transfer of Glucose, Oxygen and Carbon Dioxide in the Neurovascular Unit. J Comp Sys Bio 4(1): 101

Received Date: January 02, 2019 **Accepted Date:** April 22, 2019 **Published Date:** April 24, 2019

Abstract

Glucose and oxygen are obligatory energy substrates for the brain and their continuous supply to the neurons, as well as elimination of the end product – carbon dioxide, is of paramount importance for brain physiology and survival. Transport of these substrates from the brain capillaries to the neurons presents a challenging issue. Computer modeling of convective mass-transfer of glucose, oxygen, and carbon dioxide, taking place within the nanofluidic domain of the brain neurovascular unit, has been carried out using Kedem-Katchalsky formalism. In this model, the astrocytic endfeet aquaporin- 4 (AQP4) ensures kinetic control over the radial capillary water fluxes driven by the hydrostatic pressure gradients. The results demonstrate that convective mechanism is effective in both supplying glucose and in eliminating carbon dioxide. Oxygen transport capacity is limited to meeting the demands of the low-rate-respiring neurons across the species. The ways of enhancing the oxygen-transfer capacity of the convective mechanism have been considered. One of those is the gas oversolubility effect, observed in the nanoconfined fluids, that significantly increases the mass transfer capacity of the convective mechanism. It is suggested that the convective mass transfer mechanism and the traditional diffusion mechanism, acting together, if only in their respective domains, enhance cerebral adaptation to stress and metabolic response to brain activation.

Keywords: Computational modeling; Neurovascular unit; Nanofluidic domain; Glucose, Oxygen, Carbon dioxide; Convective mass-transfer mechanism

Introduction

The extracellular space (ECS) contains the interstitial (extracellular) fluid (ISF) involved in mass transfer of metabolic substrates, gases, signaling molecules, neurotransmitters, drugs, eliminating waste products and participating in intercellular communication. The ISF presents an external environment for the brain cells [1]. The mass transfer events taking place within the brain neurovascular unit (NVU) are extremely important for understanding brain metabolism and physiology. The NVU is a physiological and functional unit encompassing neurones, astrocytes, capillary endothelium, pericytes and extracellular matrix components. The endothelium and pericytes are part of a capillary that, together with the astrocyte endfeet membrane enveloping the capillary, act as the blood–brain barrier (BBB). The AQP4 orthogonal arrays, expressed in quantity in the astrocyte endfeet membrane, control water permeability through the BBB [2]. Topological analysis of the fluid compartments in the NVU reveals that the ECS spreads around the cells and envelopes them by sheets of 10–40 nm width. Tubular tunnels of 40–80 nm diameters connect the sheets into a network of conduits [3]. Filled with the nanoconfined interstitial fluid, this network is viewed as a nanofluidic domain where fluid movement is governed by the slip-flow principles of nanofluidic [4]. An important functional feature of the NVU is that the component cells closely interact with one another through coordinated cell-cell signaling mechanism, various chemical messengers and informational molecules, detect the needs of neuronal supply of glucose and oxygen, and trigger necessary metabolic and microvascular responses [5,6]. This interaction implies intensive mass transfer processes bound to the fluid movement in the nanofluidic domain. The brain is distinguished by high energy demands necessary for fueling neuronal activity. The major energy source is metabolism of glucose via aerobic glycolysis and mitochondrial oxidative phosphorylation [7]. The mitochondrial energy function is particularly sensitive to diminishing oxygen supply. Lowering oxygen supply rate below the minimal one is accompanied by simultaneous uncoupling of oxidative phosphorylation [8]. Complete oxygen deprivation results in loss of consciousness in a few seconds and brain death in about 5 minutes. Continuous delivery of oxygen and glucose, the obligate energy substrates, and clearance of carbon dioxide, the final waste product, are critical for brain physiology [9,10]. Commonly accepted mechanism of brain oxygenation is based on Krogh's model where mass transfer of oxygen from a capillary to the cytochrome oxidase is described by the Fick's diffusion laws [11,12]. The diffusion mechanism has been extended to include other mass-transfer events in the brain extracellular space [13-15]. Recent research into brain water metabolism suggests

convection in the ECS as an alternative mass-transfer mechanism [16-18]. In view of this it becomes important to further explore a possibility of fluid flow in the ECS along with its functional role [19]. This issue is especially important in view of the fact that there has been no presentation so far of the convective mass-transfer mechanism based on the nanofluidic principle of the fluid flow in the brain interstitial space. The aim of this work has been to model, for the first time, fluid movement in the nanofluidic domain of the NVU and to study functional capacity of the convective mechanism in mass transfer of glucose, oxygen and carbon dioxide.

Methods

The modeling of the convective mass transfer of glucose, oxygen and carbon dioxide within the NVU has been carried out in two steps. The first one deals with the mathematical presentation of the water fluxes and volumes transferred over a specified time and a cross-section area. It is based on the Kedem-Katchalsky formalism for volumetric fluid flow [20]. We used this approach in our earlier paper to evaluate the radial capillary water fluxes [4]. At the second step, the mass transfer rates for glucose, oxygen and carbon dioxide are derived.

Step 1: The equation for the radial volumetric water fluxes:

$$\ddot{u}\ddot{u}\ddot{u}\ddot{u} = \left({}^{AQP4}_{p} + {}^{\star}_{p} \right) \left({}_{a} - \frac{P_a - P_v}{L} - {}_{\text{int}} - \pi_c + \pi_{\text{int}} \right) \quad (1)$$

Where J_v, cm^3/s/mm Hg, is the volumetric flow rate per unit transfer area;

L_p^{AQP4} = 13.7 10^{-6} cm/s/mmHg, is a derived AQP4-dependent hydraulic conductivity coefficient (more on this and other parameters is in Online Recourse);

$L_p^{\star}$ is the hydraulic conductivity coefficient of the non-AQP4-dependent water transfer pathways;
S, cm^2, is the capillary radial water-transfer cross-section area;
P_a = 40.5 mmHg, is the hydrostatic pressure at the arterial end of the capillary;
P_v = 19.5 mmHg, is the hydrostatic pressure at the venular end of the capillary;
L = 0.05 cm, is the length of the capillary;
π_c = 22 mmHg, is the capillary plasma oncotic pressure;
π_{int} = 1 mmHg, the interstitial fluid oncotic pressure;
P_{int} = f (t), mmHg, is the ICP pulse pressure waveform as shown in (Figure 1). Analytical form of this function is given in Online Resource.

Step 2: Obtaining mass-transfer rates for glucose, oxygen and carbon dioxide:

(a) Mass transfer of glucose:

$$J_g = v_w K_a \quad (2)$$

Where J_g, fmol/min is the molar glucose transfer rate;
v_w ml/min, is the volume of water transferred through the capillary wall area over one minute;
K_a fmol/ml, is the molar solubility of glucose.
(b) Mass transfer of oxygen and carbon dioxide:

$$J_{O_2/CO_2} = v_w C_a \frac{p_i}{P} \quad (3)$$

Where J_{O_2/CO_2}, fmol/min is the molar transfer rate of oxygen/carbon dioxide;
C_a fmol/ml, is the molar solubility of oxygen/carbon dioxide in physiological saline under standard conditions;
P_i mmHg, is the partial pressure of the respective gas;
P, mmHg, is the standard gas pressure.

In K_a and C_a the necessary corrections have been made for the salinity, temperature and gas partial pressure. Computer simulation has been carried out using Wolfram Mathematica 10 software.

Results

A drawing of a generic NVU in Figure 1 shows a capillary and a neuron, the central anatomical and functional elements relevant to the model. The capillary is the source of glucose and oxygen for the neuron and is the sink for carbon dioxide. The drawing is

rendered to keep realistic the relative dimensions and spatial relationship of the components. The waveform of the hydrostatic intracranial pressure (ICP) in Figure 1 originates from the pulsations of the larger cerebral blood vessels and, with it systolic rise and diastolic drop, closely mirrors events of a complete heart cycle [21].

Figure 1 and 2 presents the computer simulation results in the form of the computed 3D spatiotemporal graphs demonstrating the flow of water in the NVU. The functional sections of the capillary: the filtrating section (FS), the oscillatory section (OS), and the absorbing section (AS), are distinctly defined. In our earlier research we described in some detail their role in the capillary water exchange and brain water metabolism [4].

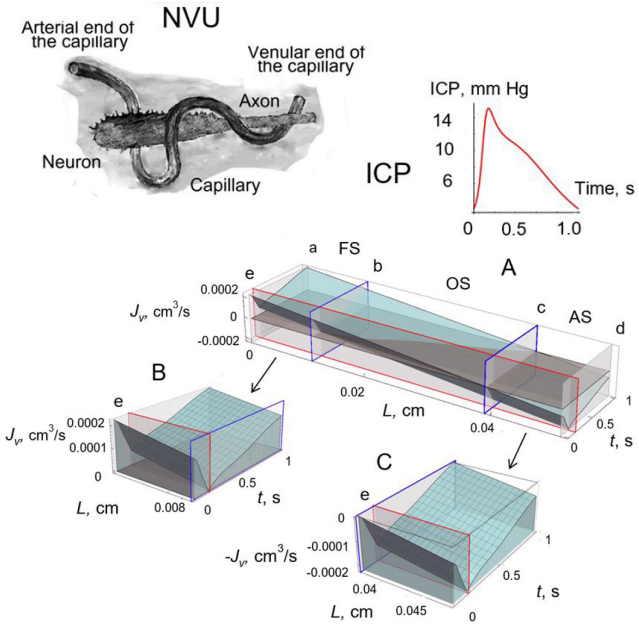

Figure 1: 3D spatiotemporal presentation of the water flow in the NVU
NVU - the neurovascular unit; ICP-the intracranial pressure waveform
A-3D graph of water exchange over a complete heart cycle, the filtrating section (FS) defined by the infinite planes a and b. The oscillatory section (OS) between infinite planes b and c. The absorbing section (AS) between infinite planes c and d. B and C present the exploded views of the FS and the AS, respectively. (More on building the computer model and the graphics can be found in Online Resource)

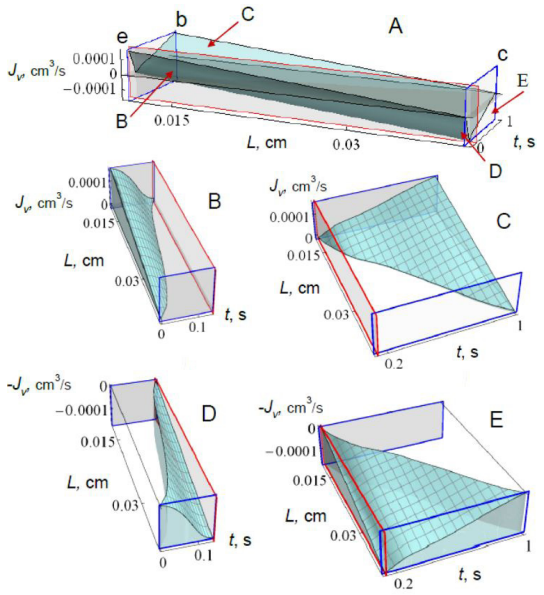

Figure 2: Computed water dynamics involving the capillary oscillatory section
A – 3D spatiotemporal graph of water flow in the OS. B-the systolic phase water filtration; C- the diastolic phase water filtration; D- the systolic phase water reabsorption; E- the diastolic phase water reabsorption. The infinite planes b and c as in Fig. 1. The oscillatory movements of fluid in the OS serve to supply, through convective mechanism, glucose and oxygen to the neuron and to remove carbon dioxide into circulation. There is a readily observed a feedback mechanism in the oscillatory movement of water between the ECS and the blood [4].

Water appearing in the FS might re-enter the circulation through the AS. This would create a convective flow of the ISF through the NVU. In the convective mass-transfer process, the positive water flux from the FS will supply glucose and oxygen to the

neurocyte. The negative water flux will be functional in removing into circulation the carbon dioxide generated in glucose oxidative metabolism. The results on water dynamics in Figure 1 and Figure 2 can be translated into the molar transfer rates for glucose, oxygen and carbon dioxide. These rates present the product of the solubility of the respective solute and the volumetric water flow rates. Figure 3 sums up the conversion data.

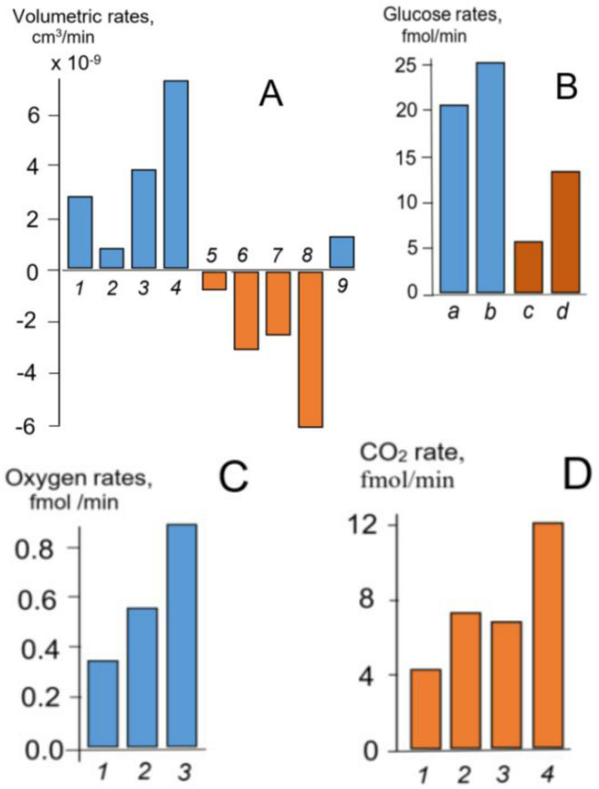

Figure 3: Computational results on volumetric water movement rates and convective mass-transfer rates of glucose, oxygen and carbon dioxide within the neurovascular unit

The figures and letters displayed with each bar along the x-axis identify the functional sections of the capillary (see infra). Simulation details could be found in Online Resource.

A. The volumetric radial water flow rates in various sections of the capillary.

The water filtration rates: 1- the FS; 2- the OS systolic phase; 3- the OS diastolic phase; 4- the FS + OS. The water reabsorption rates: 5- the OS systolic phase; 6- the OS diastolic phase; 7 - the AS; 8 - the AS + OS; 9- the total of the filtration and the reabsorption rates.

B. The molar rates of glucose supplied by the convective mechanism and the molar glucose neuronal consumption rates: **a**- Glucose supply rate within the OS; **b** - glucose supply rate within FS + OS; **c** - glucose consumption rate by the average neuron of the human brain and **d** - by the human average cortical neuron.

C. Molar oxygen supply rates by the convective mechanism:

1- the FS; 2 - the OS; 3 - the FS + OS.

D – Molar carbon dioxide elimination rates by the convective mechanism:

1- the OS; 2 - the OS + AS (at 40 mmHg of the CO_2 partial pressure). 3- the OS; 4- the OS + AS (at 70 mmHg of the tissue CO_2 partial pressure)

The experimental results presented in Fig. 3 detail information on the computed volumetric water flow rates and the substrate mass-transfer rates in various functional sections of the capillary. On the glucose mass-transfer bar chart (B) there are also given the glucose consumption rates by the average neuron of the human brain and the human average cortical neuron (bars c and d, respectively). Thus according to the model, the convective mechanism is capable of delivering glucose at the rate of 25.0 fmol/min (FS + OS). This rate is from 1.5 to 4.5 times over that of the neuronal consumption, which demonstrates high efficiency of the glucose delivery by the convective mechanism.

Neuron	Glucose, * fmol /cell/min	Oxygen,* fmol /cell/min
Across species	4.8- 24.0 [22]	0.66 - 60.0 [22,23]
Whole brain, human	5.44 [23]	27.4 [23]
Cortical neuron, human	13.20 [23]	12 .0 [24]
Cerebellar neuron, human	0.65 [23]	3.9**

Table 1: Glucose and oxygen consumption rates averaged per neuron

*±5% accuracy

**Obtained from the molar oxygen-glucose stoichiometry of six [7].

The original unites are converted into those accepted in the ongoing paper

The experimental data presented Table 1, combined with the data in Figure 3; make it possible to further evaluate the mass-transfer capacity of the convective mechanism.

The convective supply of oxygen does not look as efficient as that of glucose. Indeed, the calculated total of 0.88 fmol/min oxygen supply rate is only just adequate for the lower margin of the neuronal respiration rates across species cf. (Table 1). It is well below the demands of the human brain neurons. With all its physiological significance, it narrows the oxygen supply potential of the convective mechanism to a limited range of neurons. In the discussion section, we shall dwell on the possibilities of enhancing the oxygen supply rates.

The stoichiometry of oxygen to the carbon dioxide produced in glucose metabolism is known as a respiratory quotient and is close to unity [7]. This makes it possible to find the carbon dioxide production rates from the available neuronal oxygen consumption and to assess the effectiveness of the carbon-dioxide-removal function of the convective mechanism. As follows from Figure 3 D-2, -4, the computed maximal carbon dioxide removal rate is 6.97 fmol/min (at 40-mmHg CO_2 partial pressure) and 12.2 fmol/min (at 70-mmHg CO_2 partial pressure), respectively. These rates are from about eight to fourteen times over those of the CO_2 production by the human cerebellar neurons and just adequate in CO_2 removal in case of the human cortical neurons. This makes the convective mechanism quite capable to fully eliminate the carbon dioxide produced by various neurons.

Discussion

Brain physiology puts high demands on uninterrupted supply of glucose and oxygen to satisfy its energy demands. This energy is generated in the process of oxidative metabolism of glucose proceeding via glycolysis and the mitochondrial oxidative phosphorylation [25]. The final products are carbon dioxide and water. Continuous supply of glucose and oxygen is an obligatory precondition for brain normal activity. Glucose deprivation rapidly follows by aberrations of cerebral function while lack of oxygen results in brain damage and death in a matter of a few minutes [9,10]. Computer simulation of convective mass transfer of glucose, oxygen and carbon dioxide in the nanofluidic domain of the NVU, carried out in the ongoing paper, gives encouraging results. The modeling results demonstrate that the convective mechanism turns out to be very efficient in suppling glucose and is adequate in eliminating carbon dioxide (Figure 2). As far as oxygen delivery is concerned, the efficiency of the convective mechanism is limited to the neurons with low respiration rates. From physiological perspective, this is certainly important but puts limitations on applicability of the convective mechanism as far as the high-respiring neurons are concerned.

In modeling mass transfer capacity of the convective mechanism, we used the solubility coefficients commonly accepted for bulk water. With this, we deviate from the real properties of the extracellular fluid that in no way equal to those of bulk water. Indeed, the very confinement of water in the nanodimentional extracellular space endows it with the properties of Nano water as Nano fluid. In experiments on the brain with injected single-walled carbon nanotubes these Nano fluid properties of the ISF have been directly confirmed using super-resolution imaging [26].

Recent research on solubility of gases in nanoconfined fluids has demonstrated that bulk Henry constants no longer apply at nanoscale. There is observed instead a striking increase in solubility defined by the term "oversolubility". This may result in large uptakes of gases as high as a few hundred times over expected from bulk solubility [27]. The molecular dynamic simulations and experimental evidence demonstrated an increase of oxygen solubility in water under confinement by a factor of 5-10 [28-30]. Solubility increase by factor 15 was found for CO_2 [28].

Taking into account the oversolubility corrections, we arrive, in theory, at new oxygen supply rates ranging from 4.4 to 89.8 fmol O_2/min. This would meet all demands for oxygen over the whole range across the species of the neurocyte respiration rates.

Considering the oversolubility effect, the new elimination rate for CO_2 will be 104.6 fmol/min (at 40-mmHg CO_2 partial pressure). This value well exceeds physiological neuronal carbon dioxide production rates. Introducing the oversolubility factor makes the convective mechanism a very efficient in the energy substrates delivery and carbon dioxide removal.

The AQP4-dependent hydraulic conductivity coefficient for the BBB has been obtained on the basis of AQP4 specific dencity in the astrocyte endfeeet membrane and the single channel water permeability (Online Resource). By definition L_p^{AQP4} = 13.7 10^{-6} cm/s/mmHg rather approaches its maximum value.

Brain-fluid/blood barrier	*Lp**. $cm^3/s/mmHg/cm^2$	Assessment	Reference
AG, human	23.3 x 10^{-4}	Computational model	(2010) [31]
AG, human	15.4 x 10^{-4}	In vitro model	(2010) [32]
AG, human	18.3 x 10^{-4}	Estimation in vivo	(1991) [33]
AG, human (forward and reversed fluid movement)	1.75 x 10^{-5} 1.83 x 10^{-6}	Ex vivo model	(2008) [34]
Blood-brain barrier	0.37 x 10^{-6}	In vitro BBB astrocyte monoculture model	(2010) [35]

Table 2: The hydraulic conductivity coefficients for the brain-fluid/blood barriers
*Lp** the original units have been converted to those uniformly accepted in the ongoing paper
AG- arachnoid granulation

Table 2 gives more infromation on the brain-fluid/blood barriers permeability. It demostrates that the movement of fluids across the brain barriers is characterized by a wide range of the hydraulic conductivity coefficients exeeding L_p^{AQP4} by at least two orders of magnitude.

With the well-defined role of aquaporins in the Trans membrane water movement, it looks like they may not be monopolist in this area. Indeed, there are other cotransporters that possess an additional Tran's membrane-water-transport mode and facilitate water fluxes between various compartments of the brain [36].

Highly expressed in the capillary endothelial cells, there is a glucose-conducting channel, GLUT1, that presents, apart from transporting glucose, an example of such a water-conducting cotransporters [2]. Glucose transporter protein GLUT1, facilitates bi-directional glucose delivery from the blood to the brain across the BBB in energy-independent manner [36]. Glucose transport through the BBB is not a rate-limiting step in cerebral energy metabolism [37]. With all that, GLUT1 ensures an efficient transmembrane water movement. This, as well as functioning of various water cotransporters, may explain enhanced water permeability of the AG. High water permeability of AG membrane sets a precedent implying that the effective hydraulic conductivity might well exceed that determined by L_p^{AQP4} alone. It means that convective mass transfer mechanism might, in theory, insure higher mass transfer rates than predicted on the basis of the AQP4-induced permeability alone. A commonly accepted view on the mechanism of oxygen supply in the brain is its diffusion from the capillary to the mitochondria, driven by oxygen partial pressure gradient [38,39].The diffusion mechanism also responsible for mass transfer of glucose and carbon dioxide elimination back to the circulation. There has been also raised awareness to a possibility of convection as an alternative mechanism of mass transfer in the brain ECS [19,40]. Convective mass transfer mechanism has been the center of our long-standing research interests encompassing brain respiration, tissue oxygen mass transfer and oxygen supply to the mitochondria [4,8,40-42]. A break-through in this area came with the realization that the nanodimentionality of the ECS might be viewed not as an obstacle but as a circumstance enhancing extracellular fluid flow. Dimension of a confinement significantly modifies the flow rate of fluid. Classical nanofluidic domain, demonstrating the slip-flow effect, has characteristic dimensions of 1-100 nm [43]. This effect brings about considerable enhancement of fluid flow rate in the nanoconfined spaces [43,44]. In should be observed that the dimensionality of the ECS falls exactly into the classical nanofluidic range [45]. An interdisciplinary approach makes it possible to assume that the fast slip-flow water movement, typical for the nanodimentional conduits, might be equally applied to the biological nanospace of the ECS. We have used this approach earlier in development of a computer model of brain water metabolism [4]. We have employed this paradigm in the ongoing paper to model convective mass transfer of glucose, oxygen and carbon dioxide in the brain NVU. The diffusion and the convection might be viewed as two mass transfer mechanisms in the brain if only operating in various domains. The diffusion mechanism is expected to dominant in the brain structures where no fluid convection/advection takes place or the interstitial fluid movement is insignificantly low. It is substrate-gradient dependent and distance-sensitive.

Contrary to the diffusion, the convective mass transfer is fast, substrate-gradient independent and not so distance limited. It functions within the nanofluidic domain of the NVU: the 3D-structure of the nanodimentional channels and sheets enveloping the neurons and the glial cells. An important feature of the convective nanofluidic mass-transfer mechanism is its intimate connection with the heart activity that generates the pulsations of the intracranial hydrostatic pressure.

The developed model supports the idea of an alternative way of supplying obligatory vitally important energy substrates to the neurons through convection. The two mechanisms, acting together, if only in different domains, present important evolutionary adaptation serving to better attune metabolic responses to brain activation.

Conclusion

An optimal continouos supply of glucose and oxygen to the neurons and glial cells is vital for the physiology and survival of the brain. The supply route runs through the brain ECS that is viewed as still largely unknown territory ripe for exploration with new technologies [19].

The nunodimentionality of the ECS presents a theoretical watershed that, depending on which basic approach is chosen, offers two alternatives. Commonly used the non-slip view on the interstitial fluid movement, an intuitive thinking arising from the bulk water flow experience, leaves no choice but to use the diffusion laws to describe mass transfer in the ECS.

An interdisciplinary approach suggests using, instead, the slip-flow principles, inherent to the nanoconfined fluids. It provides theoretical grounds for developing a convective mass-transfer mechanism in the NVU. The modeling of the mass transport of glucose, oxygen and elimination of carbon dioxide, carried out along those lines, has demostrated a high functional potential of the convective mechanism. On the way there came to light a few issues that present challeges for future reseach.

Acknowledgement

The author acknowledges financial support from the National Academy of Sciences of Belarus through grant 3.09-2016-20 of State Research Programme "Convergency-2020".

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