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Abstract

The brain is divided into two parts by cellular membranes: intracellular space (ICS) and extracellular space (ECS). The brain-cell microenvironment is usually identified with the ECS. The structure of the brain resembles a porous medium. The objective of this research has been to develop quantitative methods for the study of the migration of ions in the brain, including movement between the ICS and the ECS.

In the brain-cell microenvironment, the movement of ions such as tetramethylammonium (TMA) and tetraethylammonium (TEA) is by diffusion when there is neither any electrical activity in the cells nor an externally applied electric field. The diffusion process is constrained by the geometrical factors of the medium, especially tortuosity and volume fraction. The tortuosity and the volume fraction are lumped parameters that incorporate geometrical properties such as connectivity and pore size. It is difficult to study the effects of the geometrical properties on the tortuosity and the volume fraction by using conventional methods. Therefore, we build a lattice cellular automata (LCA) model for ion diffusion within the brain-cell microenvironment and perform numerical simulations on this model by using the corresponding lattice Boltzmann equation (LBE). In the model, particle injection is introduced to match the experimental situation of ion injection through a microelectrode. As in porous media theory, the LBE model can accurately describe ion diffusion in the ECS of brain tissue.

As an application of the model, we combine the results from the simulations with porous media theory to compute tortuosities and volume fractions for various regular and irregular porous media, and a possible relationship between the volume fraction and the tortuosity also is investigated. The correlation of the results for the relationships between
the tortuosity and the volume fraction for various porous media with experimental results on brain tissues suggests that the small change of the tortuosity during ischemia, hypoxia, and postnatal development is due to the small change of the basic geometrical properties of the brain, whereas the large change of the tortuosity after x-irradiation is due to the change of the geometrical properties as a result of cell death and cell damage caused by the x-irradiation.

In the brain, potassium dynamics is constrained not only by extracellular diffusion, but also by intracellular diffusion and by active and passive transport of ions across the cell membrane. The movement of electrically charged potassium ions also is subject to electrical gradients and the spatial buffering mechanism. In addition, the geometrical factors of the brain-cell microenvironment can impose constraints on the diffusion process. It is difficult to study such a complex system using conventional methods. Therefore, we build an LBE model for this system. The evolution of the system via this model consists of three successive operations: particle injection, collision, and propagation. Those mechanisms affecting the movement of potassium are incorporated into the model by suitable choices of the injection and the collision operations, while the geometrical factors such as tortuosity and volume fraction are incorporated into the model by a suitable choice of the brain tissue as a porous medium based on our previous results for tortuosity and volume fraction. Numerical simulations on this model are performed, and the numerical results on the artificial brain as a porous medium reproduce qualitatively the behavior of potassium ions obtained from experiments with brain tissue.

As applications of the model, we study the effects of each specific mechanism on clearance of potassium within the ECS. We found that both active and passive transport of ions across the membrane affect the dispersal of injected potassium ions. However, active transport plays a more important role than the passive transport. With a very brief injection, the difference between their effects is not as large as that with a prolonged
continuous injection. The geometrical factors of the media also affect the movement of potassium. Irregularly shaped media slow down the movement of potassium since higher tortuosity makes it more difficult for the ions to move. Larger volume fraction makes the accumulated \([K^+]_o\) disperse faster. This result suggests that age-related potassium clearance is perhaps due to age-related brain geometry changes. The clearance of the accumulated extracellular potassium might depend on the specific animal and region we are studying, and some pathological conditions such as hypoxia and ischemia might affect the clearance of the accumulated ECS potassium and affect the time needed for restoring the accumulated ECS potassium to its resting level. The results also imply that young animals disperse the accumulated \([K^+]_o\) faster and consequently might prevent hypoxia, seizure, and spreading depression more efficiently than adults.

Further, the above LBE model is extended to model the migration of elevated potassium through brain tissue when there is an electric current flow. The flux is caused mainly by the iontophoretic potassium injection; the current flow is due partially to a voltage gradient through the tissue.
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Chapter 1

Introduction

The brain remains one of the least understood biological structures, due in large part to the enormous complexity of this organ. Experimental research on brain tissue is very important for our understanding of brain function. However, in some cases, an experimental approach is not enough for understanding some phenomena, and a theoretical approach is required to obtain a better understanding. In this thesis, I will build theoretical models for the movement of some ions such as potassium in the brain and will apply the models to study various phenomena in the brain which are difficult to study by experiments on brain tissue.

1.1 Neurons and glia

The brain contains many types of cells with different morphology and physiology. The most important cells in the brain are neurons (or nerve cells), each of which is bounded by a thin membrane (the plasma membrane) and has a cell body (soma). Projecting from the soma are a number of extensions of the cell known as the dendrites and the axon. The dimensions of neurons vary greatly. In general, the cell body is about 30 microns across (1 micron = $10^{-6}$ meter), dendrites are perhaps 200 or 300 microns long, and the length of the axon may be from 50 microns to several meters. The central nervous system of humans consists of about $10^{11}$ neurons of which $10^{10}$ are in the cerebral cortex.

Neurons are not isolated but rather are interconnected through axons. The axon can be considered as a tube filled with a watery solution of salts (dissociated into positively...
and negatively charged ions) and proteins, which is separated from the extracellular solution by a membrane. The internal fluid, or axoplasm, is analogous to a copper wire and the membrane to a layer of insulation around a wire, but the two systems are quantitatively quite different. For example, the axoplasm is about $10^7$ times worse than a metal wire as a conductor of electricity. Any current flowing along the axoplasm is gradually lost to the outside by leakage through the membrane due to the fact that the membrane, although relatively impermeable to ions, is not a perfect insulator.

The interconnections between neurons are at special points of contact between them, called synapses, where information transfer occurs in the nervous system. A narrow space of about 200 to 300 Å (1 Å = 10^{-10} meter) wide (synaptic cleft) separates the presynaptic membrane (the axon terminal adjacent to the dendrite) from the postsynaptic membrane (dendritic part of the synapse).

Individual neurons can encode complex information into simple electrical signals. The signals themselves consist of potential changes produced by electrical currents flowing across the cell membrane. The currents are carried by ions such as sodium, potassium, and chloride. Neurons use two types of signals: localized potentials and action potentials. The localized potentials can spread only a short distance and are graded continuously in size. These potentials depend on the passive properties of the membrane. The local potentials occur at synapses where they are known as postsynaptic potentials or simply as synaptic potentials. Synaptic potentials can be excitatory (if they tend to give rise to nerve impulses) or inhibitory (if they tend to diminish excitation). In a sensory nerve ending which is sensitive to pressure on the skin, for example, the size of the local potential (also called receptor potential) increases in relation to the magnitude of the applied pressure. There are many types of such endings or receptors, each responsive to one type of physical stimulus. The job of such a receptor is to change, or transduce, the physical stimulus into a receptor potential that then can be processed further by the
nerve cell so that information about the stimulus eventually reaches the central nervous system.

In contrast to the local potentials, the action potentials is a brief event that travels unattenuated along the axon. The action potential is an all-or-nothing event. It has a distinct threshold, and once initiated, its amplitude and duration are not determined by the amplitude and duration of the initiating event: Larger currents do not give rise to larger action potentials, and currents of longer duration do not prolong the action potential. The entire action potential sequence must be completed before another action potential can be initiated. After each action potential, there is a period of enforced silence (the refractory period) during which a second impulse cannot be initiated. If depolarization of the nerve beyond threshold is maintained longer than the refractory period, a second action potential may be initiated. In many neurons, prolonged depolarization may produce a train of action potentials that last as long as the depolarization. The frequency of the repeated action potentials is restricted by the refractory period.

Neurons are excitable cells, and they are able to transmit information down the axon by means of propagating action potentials. The action potentials propagate very fast. The speed of propagation is greater in large axons than in smaller ones. In mammals, the fastest action potentials travel in the largest fibers at a rate of about 120 m/sec (430km/hr), and therefore they are capable of conveying the information rapidly over a long distance [53].

Neurons are surrounded by satellite cells. These satellite cells are divided into two main categories: (1) neuroglial cell in the brain, which are further subdivided into oligodendrocytes and astrocytes, and (2) Schwann cells in the periphery. It has been estimated that glial cells outnumber neurons by at least 10 to 1 and make about one-half of the bulk of the nervous system [53]. Neurons and glial cells are separated from each other by narrow, fluid-filled, extracellular space. On the other hand, glial cells are linked by
low-resistance connections, i.e., gap junctions.

Through gap junctions of glia, ions and small molecules can pass directly between cells without passing through the extracellular space, and such interconnections are useful for equalizing concentration gradients that may arise. It has been shown that the low-resistance coupling between cells enables glial cells to generate currents. Although most individual glial cells do not extend over long distances, they are linked to each other by such low-resistance connections. The conducting properties of adjacent coupled glial cells, therefore, are similar to those for a single elongated cell. In a region of increased $[K^+]_o$, potassium ions enter the cell and leak out in regions of the glial cell and adjacent cells where the potassium concentration is normal. As a result, if one or several glial cells become depolarized by increased potassium concentrations in their environment, they draw current from the unaffected cells, thereby creating current flow.

Neuroglial cells and Schwann cells form the myelin sheaths around the axons—a high-resistance covering akin to insulating material around wires (axons). The myelin is interrupted at the nodes of Ranvier, which occur at regular intervals of about 1 mm in most nerve fibers. Since none of the ionic currents associated with the conducted nerve impulse can flow easily across the myelin, the ions move in and out at the nodes between the insulation. This leads to an increased conduction velocity. Glia also are involved in guiding axons to their targets during growth and regeneration [53].

One of the most distinct features of neuroglial cells compared with neurons is the absence of an axon. Also membrane properties of neuroglial cells differ in several essential respects from those of neurons. Glial cells behave passively in response to electric current, and their membrane, unlike those of neurons, do not generate conducted impulses. The glial voltage difference across the membrane (membrane potential) is greater than that of neurons and depends primarily on the distribution of potassium. In contrast, the membrane potentials of nerve cells are relatively insensitive to changes in potassium
1.2 Membrane and membrane potentials

The plasma membrane is a phospholipid bilayer with protein molecules inserted into it. Some protein molecules extend all the way across the membrane sheet; these transmembrane proteins sometimes form small-diameter aqueous pores or channels which selectively permit the passage of certain small hydrophilic molecules, such as potassium, sodium, and calcium ions. A channel which selectively passes potassium ions is called a potassium channel and a channel which selectively passes calcium is called a calcium channel. The abundance and properties of different membrane channels determines the permeability of the membrane to each ion. The states of these channels, and hence, the membrane permeabilities, may depend on the electrical difference across the membrane. In addition, the states of some membrane channels are governed by certain chemicals.

The membrane is usually very thin, its thickness is only about 50 Å. One of the most striking features of the brain cell aggregate is the vast number of interfaces provided by the plasma membrane of the cell. The total membrane area available for exchange between extra- and intracellular compartments is large in the nervous system because of the cylindrical or sheetlike process. The ratio of membrane area to extracellular volume is of the order $20 \mu m^{-1} (\mu m^2/\mu m^3)$ (page 187 in [54]). This vast membrane area allows the ions to cross the membrane quickly.

As we know, there are both organic and inorganic substances (mainly water) in the intracellular and extracellular (fluids) phases of brain, but the compositions of these two phases are different. The cations outside the cells are mainly sodium and a small amount of potassium. In the intracellular phase, the principal positively charged ion is potassium, although there is a small amount of sodium. The major anions inside cells are a class of concentration in the environment.
molecules, denoted by $A^-$, including amino acids like aspartate and glutamate.

All molecules are in a continual state of thermal agitation. Molecules in solution are relatively free to move about, so that these random vibrations disperse them evenly throughout the medium. If there is a non-uniform distribution of molecules in a solution, then these kinetic or diffusional forces cause a net migration down the concentration gradients. Thus, intracellular potassium and $A^-$ ions tend to migrate outwards through their membrane channels. Extracellular sodium and chloride ions will diffuse from outside to inside the cell. The rate at which this net migration proceeds will depend, of course, upon the concentration differences within the solution.

Since ions are electrically charged, they are also influenced by the electrical potential difference across the membrane. Positively charged ions move from a more to a less positive region, whereas anions tend to move in the opposite direction. Thus, the total flux $j_j$ of the $j$th ionic species through the membrane when both diffusional and electric field forces are present is governed by the flux equation [63]

$$j_j = -D_j \nabla C_j + \frac{Z_j C_j F}{R T} \nabla \phi$$

(1.1)

where $D_j$, $C_j$, and $Z_j$ are diffusion coefficient, concentration, and valence of the $j$th ion, respectively; $T$, $F$, and $R$ are the absolute temperature, the Faraday constant, and the gas constant; and $\phi$ is the electrostatic potential. Equation (1.1) is called Nernst-Planck equation.

1.2.1 Nernst potential

If the membrane is permeable to only one ionic species, say the $j$th ion, the condition for this ion to be in equilibrium across the cell membrane is zero net flux through its channel. In this situation, the diffusional force tending to transport ions across the membrane is balanced by the electrical force tending to move them in the opposite direction. Setting
Chapter 1. Introduction

\( j_j = 0 \) leads to [63]

\[
V_j = \frac{RT}{Z_j F} \ln \frac{[C_{j\text{o}}]}{[C_{j\text{i}}]},
\]

(1.2)

where the subscripts \( o \) and \( i \) refer to extracellular and intracellular concentration, respectively.

Equation (1.2) is called the Nernst equation. \( V_j \) is the Nernst potential or the diffusional potential of the \( j \)th ion. The ionic difference itself across the membrane produces transmembrane potential. The Nernst potential is exactly the voltage difference across the membrane required to balance the concentration difference. The constant \( RT/F \) has the dimension of volts and is equal to about 25 mV at room temperature (20°C). If we use the logarithm with base 10 (log) of the concentration ratio, the Nernst equation becomes

\[
V_j = \frac{58}{Z_j} \log \frac{[C_{j\text{o}}]}{[C_{j\text{i}}]},
\]

(1.3)

It is sometimes more convenient to use log rather than the natural logarithm.

1.2.2 Membrane potential

Different ions have different rates (permeabilities) of migration across the membrane, even when subjected to the same driving force. In the resting state, the neuron's membrane is much more permeable to potassium than to sodium although the potassium permeability is also low. Three factors jointly determine the flow of a particular ion across the membrane: concentration differences, permeability, and the voltage difference across the cell membrane, i.e., the membrane potential. The magnitude and direction of the net transfer of a given ionic species must reflect the influences of these three factors. If we use \( P_j \) to denote the permeability of the \( j \)th ion, then when multiplied by \( FZ_j \), the flux \( j_j \) becomes an electric current density \( J_j \) which then may be given by [63]

\[
J_j = \frac{P_j V F^2}{RT} \frac{[C_{j\text{o}}] - [C_{j\text{i}}] e^{VF/RT}}{1 - e^{VF/RT}}
\]

(1.4)
where $V$ is the membrane potential.

The cells contain potassium, sodium, chloride, and a large anion species and is bathed in a solution of sodium, potassium, and chloride. Other ions present in real cells, such as calcium or magnesium, are ignored here, as their contributions to the membrane potential are negligible. If the membrane potential is constant and the fluxes for the ions are not coupled, then the currents carried by sodium, potassium, and any existing leak of chloride must add up to zero, i.e.,

$$J_K + J_{Na} + J_{Cl} = 0.$$  

This leads to the Goldman-Hodgkin-Katz formula [63]

$$V = \frac{RT}{F} \ln \frac{P_K[C_K]_o + P_{Na}[C_{Na}]_o + P_{Cl}[C_{Cl}]_i}{P_K[C_K]_i + P_{Na}[C_{Na}]_i + P_{Cl}[C_{Cl}]_o} \quad (1.5)$$

for the membrane potential $V$.

Equation (1.5) looks like the Nernst equation, but with all ions included instead of just one. Moreover, (1.5) differs from the Nernst equation in that it includes the ionic permeabilities in addition to the concentration. If there is no net chloride current across the membrane, then (1.5) can be written as

$$V = \frac{RT}{F} \ln \frac{P_K[C_K]_o + P_{Na}[C_{Na}]_o}{P_K[C_K]_i + P_{Na}[C_{Na}]_i} \quad (1.6)$$

The membrane potential depends on the relative permeabilities of the cell membrane to sodium and potassium. Since in the resting state, the membrane is much more permeable to potassium than to sodium, the membrane potential is close to the Nernst potential $V_K$ of potassium. If the permeability to potassium is relatively smaller, then the membrane potential will be farther away from $V_K$. On the other hand, if the permeability to sodium is relatively large, then the membrane potential will be near the Nernst potential $V_{Na}$ of sodium. One way to express the dependence of membrane potential on concentrations of ions and membrane permeabilities is the constant field equation (1.5).
Chapter 1. Introduction

A more accurate description can be provided by a steady-state equation that includes the contribution of the active transport processes (pumps) for sodium and potassium.

1.2.3 Membrane pump

Although the net transmembrane current at rest is zero, the membrane may admit net fluxes of potassium, sodium, and chloride. A steady concentration of these ions in the cytoplasm is maintained by the sodium-potassium pump, a complicated assembly of protein subunits in the membrane which exchange external potassium for internal sodium at the expense of metabolic energy. Transport of ions across membranes which utilize metabolic energy is called active transport.

Virtually all cells maintain, at the expenditure of energy, a difference in the electrochemical potential of ions between cytoplasm and extracellular space. Active transport may be classified into two broad classes. Secondary active transport occurs when the uphill movement of ions species A is coupled to the downhill movement of ion species B in such way that the total change of free energy is negative [44]. The sodium-calcium exchange system is such an example. Under physiological conditions, the system is engaged in uphill calcium extrusion coupled to downhill influx of sodium. The primary active transport, on the other hand, utilizes a primary energy source, such as light or energy derived from ATP hydrolysis. As has become customary, the term ion pump is used as a synonym for the “primary active ion-transport system”.

Ion pumps translocate net charge across the membrane. The active-transport process for sodium and potassium involves a single protein, Na-K ATPase, that transports three sodium ions out of the cell and two potassium ions in for each molecule of ATP hydrolyzed. Other ions also are transported actively across the cell membrane with most of the transport processes being driven by the electrochemical gradient for sodium. In some cells chloride ions are transported outward and bicarbonate ions inward. Other cells
accumulate (rather than excrete) chloride, and at the same time accumulate potassium in a similar way. Inward sodium movement also is coupled to proton excretion and to calcium extrusion.

The Na, K-pump of animal cells moves ions across the membrane and thus drives an electrical current through the membrane. A pump acts as a current generator, it contributes to the transmembrane current, and it modifies the membrane potential that otherwise would be largely determined by passive ion permeabilities. The behavior of a pump adds a new dimension to the properties of a transport system. Moreover, the activity of an active transport system is not only determined by ion and substrate concentrations, but it also depends on an additional variable, the transmembrane electric field.

The pump current $I_p$ may be characterized, e.g. see [44], by its electromotive force $V_p$, conductance $G_p$, and the membrane potential $V$ as

$$I_p = G_p(V - V_p) \quad (1.7)$$

where $V_p$ may be given by a thermodynamic relation of the form (Equation 2.49 in [44]), and the pump conductance $G_p$ is determined by the rate constants of the reaction cycle. The pump conductance $G_p$ may depend, in general, in a nonlinear fashion on voltage $V$.

In an electrophysiological experiment, when an external voltage $V$ is applied to the membrane, the total transmembrane current $I$ can be measured. $I$ is the sum of the pump current $I_p$ and the passive currents $I_d$, i.e., $I = I_p + I_d$. In an analogous way, the passive (diffusive) current may be described by

$$I_d = G_d(V - V_d)$$

where $G_d$ is the conductance and the $V_d$ is the reversal potential.
1.3 Brain-cell microenvironment

The membrane separates the brain into two phases: the intracellular space (ICS) and extracellular space (ECS). The average extracellular phase spacing between cell membranes in the mammalian brain is in the range 0.01-0.04 μm (1 μm = 10⁻⁶ meter), while the cellular elements themselves have diameters ranging from 0.1 to 50 μm. The extracellular space is filled predominantly with sodium chloride solution at a strength of 150 mM or about one sixth that of sea water.

These narrow spaces between neuronal elements constitute the neuronal microenvironment which is usually called the brain-cell microenvironment. The concept of the brain-cell microenvironment actually may depend on a triadic relationship between neuron, glia, and the encompassing ECS. However, this triadic relationship has not yet been completely defined. Glia remain the least characterized element of the microenvironment, and for this reason, they sometimes are included as constituents of the microenvironment and sometimes not [54]. Glia and neurons are different in some respects; however, they have many common features. Both cells have membranes surrounding them and have membrane potentials. As in the case of neurons, glial cells and Schwann cells in culture are shown to display a variety of ion channels and pumps in their membrane [53]. Even though potassium channels usually predominate, the membranes of cultured Schwann cells and astrocytes also display sodium channels which are voltage-activated and resemble those found in neurons. Ions pumps for the transport of sodium, bicarbonate, and glutamate have been demonstrated in glial cells. Oligodendrocytes, astrocytes, and Schwann cells also display depolarizing and hyperpolarizing responses to the application of transmitters such as glutamate and GABA. Due to these similarities of glia and neurons, and since our primary interest in this thesis is the movements of ions involved in the passive state of neurons [54], [55], [59], this thesis will treat the glial cells in the same way.
category as the neurons. Thus, the brain-cell microenvironment is identified with the ECS, and the regions inside neurons and glia are the ICS.

The structure of the brain then may be thought of as a two phase porous medium. The ECS of the brain is called the pore space of a porous medium, and the ICS of the brain corresponds to the solid space of the porous medium. The membrane between the ICS and ECS are the interphase of the porous medium between the pore and solid spaces. However, the brain as a porous medium has its distinct features. The first one is the passage of some ions through the cell membrane between the ICS and the ECS. The uptake of the ions into the cells takes a very complicated form and is actually related to the membrane potential. The second is that the “solid” space, i.e., the cytoplasm of cell, is not rigorous solid space. Some ions can cross the membrane through their channels. Once the ions have passed through the membrane, they will freely diffuse within the ICS. Some ions can cross the membrane back into the ECS. The third one is the change in the structure with time during the movement of the ions. The movement of ions is always accompanied with water movement which usually leads to the swelling of cells. This last feature is too complicated to be considered here. In this thesis, we assume that the structure of the brain doesn’t change with time.

As the brain has evolved, the total brain volume and the packing density of neurons and their protoplasmic extensions, dendrites, and axons, have increased due to the necessity for more interconnections. The close proximity of neuronal elements in the brain and the narrowness of the intercellular spaces provides a basis not only for the interaction between the cells themselves, but also between the elements and their microenvironment.

The dense aggregation of cells within the central nervous system inevitably leads to a high degree of interdependence between the cells and their surroundings. As the

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1This use of the word “pore” should not be confused with its common use in neurophysiology to describe a membrane “channel”.

cellular elements pack closer together, the area of the cellular surface relative to the ECS volume becomes greater. Consequently, the influence on the microenvironment of the passage of substances across membranes and the reciprocal influence of the environment on membrane behavior become amplified.

Chemical substances, ions, neurotransmitters, and enzymes that can cross the cell membranes can easily find their way through the ECS to adjacent cellular elements. The transmission flux of ions that is produced by neuronal and fiber activity will modify the ionic composition of the fluid in the surrounding ECS. During an action potential or during excitatory postsynaptic potentials, $\text{Na}^+$ or $\text{Ca}^{2+}$ enters the intracellular compartment and $\text{K}^+$ leaves it. In this way the microenvironment can ensure nonsynaptic communication between the relevant neurons. Signals can be coded by modulation of the chemical composition of the ECS in the vicinity of the cell membrane and does not require the classic connection by axons, dendrites, and synapses. This concept also includes the transport of chemical substances through the intracellular spaces of cellular elements like glial cell, so that the spatial relationship between nerve cells acquires new significance. Studying the dynamic structure of the brain-cell microenvironment and studying the migration of the substances within the brain-cell microenvironment are very important for improving our understanding brain function. These are the main objectives of this thesis.

One of the most significant technical developments in probing the migration of substances within the microenvironment is the ion-selective micropipette (ISM) to monitor directly the variations in ionic activity in the immediate vicinity of brain cells [56]. ISMs are miniature potentiometric sensors whose main component part is an electrochemical membrane. The first ISMs were made of ion-selective glass [75]. Their disadvantage was their relatively low selectivity and large size of the active surface. Currently, ISMs are much better and are the most perfect sensors for measuring the dynamic changes in the
concentration of biologically important ions in vivo. When the ISM is inserted into neural tissue, it records not only electrical potential generated mainly by free ion concentration but also all types of electrical activity (e.g., membrane and action potential).

Substances migrating in the brain-cell microenvironment may be classified by their potential roles as "informational" or "energetic" [58], [59]. The "energetic" indicates the movement of metabolic substrates, products, and by-products responsible for maintenance of the living organism. The migrations of energetic substances are usually involved with relatively large fluxes. Thus, energetic substances are characterized by their role in the life of a cell as well as by their relatively high concentration. Typical "energetic" substances are oxygen, carbon-dioxide, and glucose. In contrast, informational substances can be defined by the characteristic that they act on cells at low concentration to change the system and cellular behavior. Informational flows are not destined to provide fuel, but rather to change the state or behavior of the recipient, that is, to signal or communicate. Such a class of substances comprises mainly simple ions such as $K^+$, $Na^+$, $Cl^-$, $Ca^{2+}$.

It is very important to recognize that this classification is not distinctively clear. The ions $Na^+$ and $Cl^-$ are clearly involved in the energetics of transport and they are present in large amounts. The ions $K^+$ and $Ca^{2+}$ are more obviously informational in that they occur at relatively low concentrations in the ECS and may be involved in some form of signaling. Most of this thesis will be concerned with the migration of informational substances within the brain, especially the migration of potassium.

### 1.4 Migration of potassium in brain

Potassium can accumulate temporarily in the ECS. During neuronal and fiber activity or during excitatory postsynaptic potentials, potassium ions leave the ICS and enter
the ECS, which causes an elevation of the extracellular potassium concentration. The increase of extracellular $K^+$ concentration $[K^+]_o$ is probably due partly to fluxes during action potentials and partly to increases of the permeability produced by synaptic transmitters [22]. The intracellular concentration of $K^+$ in neuronal elements exceeds the level of $[K^+]_o$ in non-stimulated brain or spinal cord of vertebrates by a factor of approximately 25-45, and the volume of the ICS is 4 times larger than that of the ECS. Even a small fraction of intracellular $K^+$ can substantially change $[K^+]_o$ in the narrow intercellular clefts which are 20-30 nm wide.

The $[K^+]_o$ accumulates in the ECS during hypoxia [66] and ischemia [62]. Through measurements in the hippocampal CA1, CA3, and cortical slices during ischemia, Nicholson’s group [62] found that ischemia causes the extracellular concentration to rise to 45 mM in CA1, 12 mM in CA3, and 32 mM in cortex from the baseline of 5 mM. During hypoxia, the extracellular potassium $[K^+]_o$ rose from an average baseline of 5.1 mM to 7-10 mM [66]. Application of drugs, such as the application of GABA to rat dorsal root ganglia and application of serotonin in the rat hippocampal slices, elevate $[K^+]_o$[75]. A direct iontophoretic point injection of potassium ions into the ECS also can lead to a temporary accumulation of potassium ions in the ECS [32],[33],[49].

These changes of $[K^+]_o$ constitute disturbances of the brain-cell microenvironment that may significantly affect the balance of the interactions between neurons even with normal physiological activity. The accumulated $[K^+]_o$ modifies the ionic composition of the fluid in the surrounding ECS. The accumulated $[K^+]_o$ depolarizes neurons and nerve fibers in the vicinity, affects their excitability and transmitter release, and modulates the efficacy of impulse transmission. The increased $[K^+]_o$ also depolarizes glial cells and affects their function. If $[K^+]_o$ rises to a pathological level, it can result in a process known as 'spreading depression' [34], [45], [80]. The increase of $[K^+]_o$ has been suggested to be a cause of epilepsy [25]. In several studies, for example, perfusion of the cortex
with solutions containing high K⁺ concentration (8.8-16.0 mmol l⁻¹) has been shown to induce hippocampal epileptic activity [25].

The intracellular K⁺ released by active neurons must be restored, and the activated Na/K⁺ pump is the major mechanism involved in the restoration of intracellular ionic composition. In discharging neurons, the active transport is stimulated by the increase of the intracellular sodium concentration so that the sodium is pumped out of and potassium is pumped into the cell. The pumping rate is proportional to the intracellular sodium for a given [K⁺]₀. The active transport stimulated in this way may account for the lowering of [K⁺]₀ below the initial resting level, i.e., the “undershoot” observed by, for example, Heinemann et al. [32], [33].

The active transport also may be stimulated by a rise of the extracellular potassium concentration itself [54]. The effect of [K⁺]₀ on pumping may be more effective when [K⁺]₀ is higher, and the effect is more marked for high K⁺ concentrations in glia than in neurons. The active transport will aid the clearance of the accumulated [K⁺]₀. In this case, the pump is not expected to lower the [K⁺]₀ level below the initial resting baseline.

The accumulated [K⁺]₀ leads to the disturbance of K⁺ concentration difference across the membrane, and since the potassium can cross the membrane through its channel, the passive transport due to diffusional force across the membrane will affect the redistribution of the temporarily accumulated [K⁺]₀.

When a local build-up of [K⁺]₀ occurs in neural tissue, depolarization of nerve and glial cells may cause current to flow through the glial cells. The current may serve to redistribute K⁺ from the extracellular site where its concentration is high to the areas where its concentration is lower. This concept that K⁺ enters the glial cells in one region and leaves it elsewhere has been called the “spatial buffer mechanism”. The basic membrane properties of glial cells make them suitable for the development of current loops through their cytoplasm and the extracellular space to redistribute K⁺ from one
region of the ECS to another region of the ECS where $[K^+]_o$ is normal. First, glial cell membranes are almost exclusively permeable to $K^+$ and sensitive to changes of $[K^+]_o$. Second, the glial cells are electrically coupled. Their specific membrane resistance is high when compared to that of neurons, but the interconnection (gap junction) resistance between glial cells is low which permit $K^+$ to move through the glial cells.

Since potassium can cross the membrane through its channels, a concentration gradient in the ECS will lead to an intracellular gradient as well. Thus, cytoplasmic diffusion may contribute to flux through the tissue. Small cells, however, may contribute to uptake but not significantly to diffusion, if they lack cell processes extending far in the direction of the concentration gradient.

Whenever a $K^+$ gradient is established during neuronal activity, the ions move from the region with a higher concentration to that with a lower concentration. The extracellular space is large enough to permit the passage of the hydrated $K^+$. The ECS diffusion may contribute to the clearance of the accumulated $[K^+]_o$. However, the $K^+$ does not move in the extracellular space as in a free, aqueous solution. The ECS diffusion is constrained by the geometries of the brain tissue. Firstly, through the cellular obstructions of the intercellular clefts and secondly, through the restricted extracellular space, the geometry of the brain will affect the ion diffusion within the ECS.

Exchange between extracellular fluid and the blood constitutes the means by which the normal baseline composition of the brain fluids is maintained constant over long periods of time. However, it seems unlikely that this exchange can affect the local ionic disturbance arising in the extracellular space during neuronal activity [54], [76]. The exchange between blood and extracellular fluid does not contribute to $K^+$ clearance, at least for a relatively short time period. When $[K^+]_o$ rises to high values, the redistribution observed is due to other mechanisms, mainly the uptake by neurons and glial cells.

The dispersal of the accumulated extracellular potassium is affected by the ECS and
ICS diffusions, by passive and active transport across the membrane, by the spatial buffering mechanism. The aim of this thesis is to build a theoretical model for the dispersal of the potassium and to study the migration of the increased extracellular potassium \([K^+]_o\) when the increased \([K^+]_o\) is brought about by iontophoretic injection. The model is intended to incorporate all these mechanisms.

The extracellular diffusion is one of the mechanisms imposing constraints on the dispersal of potassium. The ECS diffusion itself is of great importance in studying the neuronal population. Therefore, we first study the ECS diffusion subject to the complicated ECS geometries.

1.5 Diffusion within the extracellular space

Substances move through the brain interstices almost entirely by diffusion when there is no external applied electrical field. Diffusion is an inescapable process that influences and constrains numerous facets of brain function. The diffusion characteristics of the brain-cell microenvironment are very important in analyzing the physiology of neuronal populations. Since the migration of potassium and calcium can cross the membrane, their migrations within the ECS are affected not only by the ECS diffusion, but also by many other factors such as active and passive transport and intracellular diffusion. Their movements are involved with voltage changes within the ICS and ECS. To study the pure diffusion phenomena within the ECS and to study the dynamic structure of the brain-cell microenvironment, these ions are not good candidates. The most suitable ions must not be taken up into cells appreciably during a short period of time, and they must be nontoxic to the brain. Ions that satisfy these criteria are tetramethylammonium (TMA) and tetraethylammonium (TEA). The ions TMA and TEA do not cross the cell membrane. After they have been injected into the ECS, they stay in the ECS and diffuse.
in the ECS. Nicholson and his colleagues made an extensive series of measurements with TMA and TEA in the cerebellum of the rat, the cerebellar slice of the guinea pig, the isolated cerebellum of the turtle, etc., using iontophoresis and pressure injection [54], [55], [62], [60].

Despite the fact that the average spacing between cells may be no more than 20 nm [54], the mean free path of an ion at the typical ionic strength of the mammalian nervous system is only about 0.01 nm. This represents the distance traveled between collisions with other molecules. Almost all these collisions actually take place with water molecules since the concentration of water is 55 M [58]. Thus an ion rarely encounters a cell membrane and behaves most of the time as though it were in a free medium. This means that on a microscopic scale the behavior of the ion within the ECS may be given by Fick's law

\[ J = -D \nabla C \]  

(1.8)

where \( J \) is the extracellular flux, \( C \) is the substance concentration, and \( D \) is the diffusion coefficient of the substance. Thus the conservation of the substance is governed by

\[ \frac{\partial C}{\partial t} = -\nabla \cdot J + q \]  

(1.9)

within the ECS which gives the equation

\[ \frac{\partial C}{\partial t} = D \nabla^2 C + q \]  

(1.10)

where \( q \) is the source term brought about by the experiment such as ion injection from a micropipette.

The membrane boundary condition, i.e., the conditions along the membrane boundary, for the diffusion process (1.10) within the ECS depends on the specific ions under consideration. For example, TMA and TEA do not cross the membrane, so the membrane boundary condition is simply the zero-flux condition. For other ions such as potassium,
the membrane boundary conditions are more complicated and actually are related to the concentration and potential differences across the cell membrane.

In principle, one could solve the diffusion equation (1.10) subject to the membrane boundary condition with the complicated membrane boundary geometries if we know the geometries. The geometries of the brain-cell microenvironment could be revealed by sufficiently high-power electron micrographs [58]. The difficulty lies in solving the diffusion equation subject to conditions that have to be defined on geometrically complex membranes. When studying the migration of potassium, we need to account for events at the membrane boundaries which are complicated and involve some form of transport across the membrane. Solving the governing equation is even more difficult. A direct study of such problems using conventional methods is impossible.

To study the diffusion within the ECS and the dispersal of accumulated potassium, what we need are methods of incorporating the membrane boundary conditions so that they can be approximated in some overall form that retains the essential features of the structure. The method should be relatively simple and simultaneously take care of both the membrane boundary conditions and the complex membrane geometries. Fortunately this type of problem has been encountered in certain areas of applied chemistry and in geophysics, especially in the area of flow in a porous medium. To avoid the difficulty, several methods often have been used, including the homogenization method, the volume averaging theory used by Nicholson and his colleagues, a network technique [17], [40], and the lattice gas cellular automata (LCA) method and the corresponding lattice Boltzmann equation (LBE) method [15], [16] used by Chen et al. [10] and Rothmann and his group [26], [69]. These latter techniques are to be developed in this thesis for application to diffusion of ions in the brain.

The homogenization method is a mathematical method for dealing with a multi-scale system. A general discussion of the asymptotic analyses of periodic structures is
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given by Bensoussan et al. [7]. The homogenization method was applied to Stokes flow through periodic structures by Sanchez-Palencia [71]. Later, Ene and Poliservski [19] expanded and applied the principles to the study of natural convection in porous media. The method is based on the study of periodic solutions of partial differential equations and on the asymptotic behavior of these as the period tends to zero. The hypothesis of a periodic structure allows for rigorous treatment of problems such as fluid flow in porous media and other microscopic systems. The asymptotic solution expansion is made using a small parameter $\epsilon$ that is the ratio of the pore (the representative elementary volume) length scale to the system length scale $L$, i.e., $\epsilon = l/L$, where $l$ is the linear dimension of the periodic structure (unit cell). The asymptotic process $\epsilon \to 0$ represents the transition from microscopic to macroscopic phenomena. Homogenization is a simultaneous description of microscopic as well as macroscopic phenomena.

The homogenization method also has been used by Neu and Krassowska [52] to covert a microscopic system, consisting of the Laplace equation for the potential in the ECS and ICS and the electrical properties at the membrane, into an averaged, continuum representation, consisting of two reaction-diffusion equations. The homogenization method is similar to local volume averaging (Chapter 2). However, the homogenization method requires that the microscopic structure of the considered tissue be periodic. This method cannot be directly applied to ion movement in the brain unless the brain cells are assumed to be in a periodic arrangement.

A network approach reduces the disordered nature of porous media to an approximation onto which wide ranges of porosity, pore-size distribution, pore structures, and pore connectivity can be mapped. Dullien [17], Lin and Cohen [48], and Koplik et al. [40] provide a conceptual framework by which pore spaces can be mapped into equivalent networks. The irregular structure of a porous medium is represented by an ordered network of bonds and nodes in which all relevant local properties (details of pore space
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and transport process) are assigned to the bonds. For example, resistance to flow can be mapped onto an electrical resistor analog. Transport properties then are calculated on these network approximations.

For a two-dimensional brain, we can choose a symmetric triangular lattice as an approximation. On the one hand, we can let particles go along lattice bonds and collide at the nodes according to some updating rule. For instance, we could adapt the rule that the particles move by pure diffusion. On the other hand, we can think of the lattice as a network and assign resistance to the bonds, electrical potentials at the various nodes, and let the current be conserved at each node as in [79].

This network approach is a excellent idea, but rather than carrying out a detailed study of this problem, we first study the flow of ions through the porous medium of the brain by using the volume averaging theory and the LCA method. Using the LCA method has some advantages; the most important one of which is that in arbitrarily complex membrane geometries, accurate calculations of microscopic flow are practical. Another advantage is that the LCA can provide a detailed and a visible movement of the ions by using the computer.

This thesis is divided into four parts. The first part consists of Chapters 2 and 3. In Chapter 2, we give a brief review of the volume averaging method and the work of Charles Nicholson and his colleagues. In Chapter 3, we will give a review of the lattice gas cellular automata method and the corresponding lattice Boltzmann equation method, especially the FHP model. The second part is Chapter 4 in which we build a lattice gas cellular automata model for ion diffusion within the extracellular space, and use the model to study the effect of the geometrical properties on the tortuosity and volume fraction. The third part includes Chapters 5 and 6 in which we build lattice gas cellular automata model for potassium movement in both the intra- and extracellular spaces. As an application of the corresponding lattice Boltzmann equation model, we study the
effect of various mechanisms on potassium movement. The fourth part is Chapter 7 in which general conclusions of this thesis are drawn and future research is proposed.
Chapter 2

Volume-Averaging Method

If one wishes to characterize the concentration of a particular ion which occurs only within the extracellular phase, then as one moves continuously along any given direction, the ionic concentration will fluctuate between the local extracellular value and the intracellular value, zero. This will lead to a discontinuous concentration profile and consequently the derivative will not behave in a tractable manner. To avoid this mathematical problem, Nicholson and Phillips in 1981 [57] used the volume averaging theory developed by Whitaker [81] and others [24], [47].

2.1 Volume-averaging

Letting $\phi$ be some point quantity in the pore space (the ECS), such as the extracellular concentration $C$ and flux $J$, and be zero in the solid space (ICS), we define the volume (phase) average of $\phi$ at point $x$ as

$$<\phi> = \frac{1}{V} \int_{V_0} \phi d^3y = \frac{1}{V} \int_V \phi d^3y$$

where $V$ is the volume of a suitable averaging region of brain with its centroid at point $x$, $V_0$ is the extracellular component within $V$, and $d^3y$ is the differential volume element.

$V$ is called the representative elementary volume (REV) [4], which is a characteristic property of the porous medium. $V$ must be properly chosen in accordance with the particular medium. If $V$ is too large, the averaged quantity $<\phi>$ does not vary much with the independent space variable, i.e., $<\phi>$ is approximately a constant. This is
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certainly not the situation we want to study. If \( V \) is too small, the averaged quantity \( < \phi > \) may still fluctuate with the local extracellular and local intracellular values. The \( < \phi > \) is not smooth enough to be differentiable\(^1\), which is not the goal of the averaging. Here \( V \) remains fixed at all times while \( V_0 \) could vary with position. In many cases, \( V_0 \) could vary with time, but in this thesis, we will assume that the geometry of the ECS of the brain is always fixed, so \( V_0 \) is independent of the time.

The extracellular volume average or the intrinsic phase average of \( \phi \) is defined as

\[
< \phi >_0 = \frac{1}{V_0} \int_{V_0} \phi d^3y. \tag{2.2}
\]

In contrast to the volume average, the intrinsic phase average is formed by integrating only over the ECS. It is understood that it is the intrinsic phase average of the concentration, not the phase average, that is relevant to the concentration actually measured by an ISM.

The volume fraction, \( \alpha \), of the extracellular space is defined as the ratio of \( V_0 \) to \( V \), i.e.,

\[
\alpha = \frac{V_0}{V} = \frac{< \phi >}{< \phi >_0}. \tag{2.3}
\]

If we define the indicator function (the characteristic function) of the ECS as

\[
\gamma_0(x) = \begin{cases} 
1 & \text{if } x \text{ is in the ECS}, \\
0 & \text{otherwise},
\end{cases} \tag{2.4}
\]

then we have

\[
\alpha = < \gamma_0 > = \frac{1}{V} \int_V \gamma_0 d^3y.
\]

In order to use averaged theory effectively, as developed by Whitaker [81], Gray and Lee [24], and Lehner [47], it is required to introduce the notion of scale. First, one needs a

\(^1\)This definition of average cannot guarantee that the averaged quantity \( < \phi > \) is differentiable; however, this definition is still popularly in use by engineers, and it was believed or assumed that the averaged quantity has this property.
microscopic distance, \( d \), which is a representative distance over which significant variation in the point quantity, \( \phi \), takes place; then one needs a macroscopic length, \( L \), which is a representative distance over which significant variation in the volume averaged quantity, \( <\phi> \), takes place. For averaging to be meaningful, it must take place over a distance, \( l \), which is a characteristic length of the averaging volume \( V \) of the porous medium and is required to satisfy

\[
L \gg l \gg d.
\]  

Usually, one associates \( d \) with the mean pore diameter and \( L \) with the dimension of the total size of the medium under consideration. In the brain, \( d \) ranges from 0.01 \( \mu m \) to 0.04 \( \mu m \), which is the order of the spacing between membranes within which essentially free diffusion occurs. \( L \) is 1 \( mm \), for example, the total size of a homogeneous brain region used in [57], and \( l \) is about 6 \( \mu m \).

With the restriction (2.5), Whitaker [81] had shown

\[
< <\phi> > = <\phi> + O(<\phi>(l/L)^2)
\]

which means that the average of the average is equal to the average. Whitaker also had shown some interesting results, for example, the volume average is equal to the area average and the volume fraction is essentially equal to the three planar fractions if the medium is homogeneous. If \( V \) is a cube of volume \( l^3 \), for instance, and \( A(j,k) \) is the area of magnitude \( l^2 \) in \( V \) parallel to the \((j,k)\) plane, \( j,k = x,y,z, j \neq k \), then the planar fraction is defined as the ratio of the area of the extracellular part in \( A(j,k) \) to the total area of \( A(j,k) \).

In developing the averaged form of the basic equation, one has to deal with derivatives of point functions and to explore the problem of averaging derivatives of functions since one usually is interested in obtaining derivatives of averages rather than averages of
derivatives. Several useful relationships between derivatives of averages and averages of derivatives for point functions can be found in [24], [81].

One of these useful relationships is the general transport theorem which states that

$$\int_V \frac{\partial \phi}{\partial t} d^3y = \frac{\partial}{\partial t} \int_V \phi d^3y - \int_A \phi \mathbf{w} \cdot \mathbf{n} d^2y$$ (2.6)

where \( \mathbf{w} \) is the velocity of the surface \( A \) which encompasses the volume \( V \), and \( \mathbf{n} \) is the unit normal vector directed outward from the extracellular space.

Actually, from formula (8) of Gray's paper [24], equation (2.6) takes the form

$$\int_V \frac{\partial \phi}{\partial t} d^3y = \frac{\partial}{\partial t} \int_V \phi d^3y - \int_M \phi \mathbf{w} \cdot \mathbf{n} d^2y$$ (2.7)

where the surface integral is taken over the interface \( M \), the membrane between the ICS and the ECS within \( V \).

From the general transport theorem, one can derive the averaging theorem [24], [81]

$$\langle \nabla \phi \rangle = \nabla \langle \phi \rangle + \frac{1}{V} \int_M \phi \mathbf{n} d^2y.$$ (2.8)

In general, the above formula is true for scalar, vector, and matrix quantities.

### 2.2 Effective diffusion equation for the diffusion of TMA and TEA in ECS

Fick’s first law (1.8) and the conservation equation (1.9) are valid only over a space scale \( d \). To enlarge the region of validity to the scale \( L \), one uses the volume averaging method. Averaging Fick’s first law (1.8), one obtains

$$\langle \mathbf{J} \rangle = -D \langle \nabla C \rangle.$$ (2.9)

The averaging theorem (2.8) gives

$$\langle \nabla C \rangle = \nabla \langle C \rangle + \frac{1}{V} \int_M C \mathbf{n} d^2y.$$ (2.10)
If there is not any absorption along the interfaces (membrane) and these interfaces are impermeable to the substance being studied, then we have a zero-flux membrane boundary condition, i.e.,

\[ \mathbf{J} \cdot \mathbf{n} = 0 \quad \text{on} \quad M; \quad (2.11) \]

so long as the medium is homogeneous, Lehner [47] had shown that

\[ \frac{1}{V} \int_{M} C nd^y = (\mathbf{K} - \mathbf{I}) \cdot \nabla < C > \quad (2.12) \]

where \( \mathbf{I} \) is the identity, and \( \mathbf{K} \) is a positive definite symmetric matrix. In the case of a free medium which has no cellular elements, \( M \) is an empty set and \( \mathbf{K} = \mathbf{I} \). In a complex porous medium like the brain, \( \mathbf{K} \) generally differs from \( \mathbf{I} \). In [47], \( \mathbf{K} \) is called the "intrinsic conductivity" of the porous medium. \( \mathbf{K} \) is a dimensionless quantity.

Combining (2.9), (2.10), and (2.12), one obtains the following macroscopic Fick's law

\[ < \mathbf{J} > = -D \mathbf{K} \cdot \nabla < C > \quad (2.13) \]

which is valid on a larger scale. This is a very important step since it essentially absorbs the local structure of the medium into the quantity \( \mathbf{K} \). In an isotropic medium, \( \mathbf{K} \) is a positive scalar multiplied by the identity matrix, so Nicholson and Phillips [57] wrote it as

\[ \mathbf{K} = \frac{1}{\lambda^2} \mathbf{I} \quad (2.14) \]

where \( \lambda \) is called the tortuosity, which had been introduced frequently into the biological diffusion literature. The tortuosity \( \lambda \) is not less than one and is thought of as representing the increased path length that a diffusing ion traverses as a result of the presence of cellular obstructions. In [47], the surface integral (2.12) was defined as the tortuosity vector. This later definition of the tortuosity indicates that the tortuosity is concentration-dependent.
Chapter 2. Volume-Averaging Method

Averaging the material conservation law (1.9), one gets
\[ \langle \nabla \cdot \mathbf{J} \rangle + \langle \frac{\partial C}{\partial t} \rangle = \langle q \rangle. \] (2.15)

Again, the averaging theorem gives
\[ \langle \nabla \cdot \mathbf{J} \rangle = \nabla \cdot \langle \mathbf{J} \rangle + \frac{1}{V} \int_M \mathbf{J} \cdot \mathbf{n} d^2y. \] (2.16)

Thus, with the zero-flux condition (2.11), one obtains
\[ \langle \nabla \cdot \mathbf{J} \rangle = \nabla \cdot \langle \mathbf{J} \rangle. \] (2.17)

From the general transport theorem (2.6), one obtains
\[ \langle \frac{\partial C}{\partial t} \rangle = \frac{\partial \langle C \rangle}{\partial t} - \frac{1}{V} \int_M C \mathbf{w} \cdot \mathbf{n} d^2y. \]

If the phase interface is stationary, i.e., the membrane does not move, then
\[ \langle \frac{\partial C}{\partial t} \rangle = \frac{\partial \langle C \rangle}{\partial t}. \] (2.18)

Thus, combining (2.15), (2.17), and (2.18) with the macroscopic Fick's law (2.13), one obtains the following macroscopic effective diffusion equation with averaged quantities
\[ \frac{D}{\lambda^2} \nabla^2 \langle C \rangle_0 + \frac{\langle q \rangle}{\alpha} = \frac{\partial}{\partial t} \langle C \rangle_0 \] (2.19)

for the concentration of the substance which is governed by (1.10).

Thus, studying diffusion in the brain-cell microenvironment is equivalent to that in a simple medium with an effective diffusion coefficient \( D_e \equiv D/\lambda^2 \) obtained by scaling the diffusion coefficient \( D \) by the square of the tortuosity and with an altered source term \( \langle q \rangle /\alpha \). The effective diffusion coefficient \( D_e \) is affected by the pore structure, i.e., when the tissue is viewed as a continuum, the effective diffusion coefficient is obtained by averaging over many cells. The effective diffusion equation (2.19) can accurately describe
the migration of several ions and neurotransmitters, such as TMA and TEA, since the absorption of these ions into cells is very slow, which means that condition (2.11) holds approximately.

If we use \( D_e \) to denote the effective diffusion coefficient of the substance when tissue is viewed as a continuum, then the tortuosity could be formally defined as the square root of the ratio of the diffusion coefficient within the ECS to the effective diffusion coefficient, i.e., \( \lambda = \sqrt{D/D_e} \), with the square root appearing because of the interpretation of \( \lambda \) in terms of the increased path length. There are several different definitions of the tortuosity in the literature. Bear [5] defines tortuosity as \( \lambda = D_e/D \), while Schultz and Armstrong [74] use \( \lambda = \alpha D/D_e \). Here we will use Nicholson and Phillips’ definition, i.e., \( \lambda = \sqrt{D/D_e} \).

As the movement of ions is affected by the geometry of the extracellular space, it is obvious that the diffusion of ions in the extracellular space must be slowed down. The geometry of the ECS affects the movement of ions in two characteristic ways: through the tortuosity \( \lambda \) of the intercellular cleft and through the restricted extracellular space (volume fraction \( \alpha \)). The long-chain glycoproteins and glycolipids, which are present in cell membranes, can carry negative charges and probably also affect the migration of ions. These effects, especially the geometrical effects, have been successfully incorporated into the effective diffusion equation model (2.19) through the tortuosity and the volume fraction parameters.

The derivation of (2.19) will still go through because (2.13) still holds for a more general absorbing condition

\[
\mathbf{J} \cdot \mathbf{n} = k(C_0 - C_i),
\]

(2.20)

instead of (2.11) where \( k \) is the mass transfer coefficient or non-specific uptake of the substance and \( C_0 - C_i \) is the driving concentration difference between the actual concentration \( C_0 \) and a mean equilibrium concentration \( C_i \) along \( M \).
Nicholson and Phillips applied the principle of reciprocity [65], solved a new equation
\[
\frac{D}{\lambda^2} \nabla^2 U + \frac{q}{\alpha} = \frac{\partial U}{\partial t}
\] (2.21)
in a simple medium, arrived at
\[
< C >_0 = < U >= U,
\]
and got the following approximate solution of (2.19) for small \( l \):
\[
U(r, t) = \frac{Q \lambda^2}{4\pi D \alpha r} erf\left(\frac{r \lambda}{2\sqrt{D t}}\right)
\] (2.22)
where \( Q = \int v q d^3x \) is the number of ions released per unit time from the source; \( r \) is the distance from the source.

The ion-selective microelectrode permits the direct examination of ion diffusion in the brain and monitoring of ionic concentration in real time at a specific point in a given tissue; thus, by fitting the experimental data to a solution (2.22) of the effective diffusion equation (2.19) at two different times, the parameters \( \lambda \) and \( \alpha \) can be computed [57].

### 2.3 Measurement of volume fraction and tortuosity for various brain tissues

The values of volume fraction and tortuosity for rat cerebellum were determined from the measurements of iontophoretically induced diffusion profiles of TMA. By combining (2.22) with their experimental data (from point iontophoresis), Nicholson and Phillips [57] determined the parameter values, and showed that the volume fraction \( \alpha \) was 0.21±0.02 the tortuosity \( \lambda \) was 1.55±0.05. Volume fraction and tortuosity also have been measured for many other brain tissues [58], [59]. For example, the volume fraction and tortuosity for guinea pig cerebellum are 0.28±0.02 and 1.84±0.05, for turtle cerebellum, they are 0.21±0.01 and 1.65±0.02, for skate cerebellum they are 0.25±0.02 and 1.62±0.02, respectively.
Volume fraction and tortuosity were measured during normoxia and hypoxia in slices of rat neostriatum by Rice and Nicholson [66]. Under normoxia conditions, the average volume fraction was 0.21 and tortuosity was 1.54 which are well within the range of average values reported earlier for the cerebellum of rat. The average values for volume fraction during hypoxia was 0.13, a 38% decrease of the average value. Hypoxia induces decreases in $\alpha$ and for as long as the hypoxic period continues, the volume fraction continues to decrease. In contrast, the tortuosity was unaffected by hypoxia.

In 1995, Perez-Pinzon et al. [62] studied the changes in extracellular potassium concentration, the volume fraction, and tortuosity in rat hippocampal CA1, CA3, and cortical slices during ischemia. During normoxia the volume fractions were 0.14, 0.20, and 0.18, and tortuosities were 1.50, 1.57, and 1.60 in CA1, CA3, and cortex, respectively. During ischemia the volume fraction decreased to 0.05, 0.17, and 0.09 in CA1, CA3, and cortex, respectively. Only in CA3 did the tortuosity change significantly by increasing to 1.75. The ischemia caused the potassium concentration to rise to 45 mM in CA1, 12 mM in CA3, and 32 mM in cortex from a 5 mM baseline.

Extracellular volume fraction and tortuosity depend on the geometry of the brain tissue. Different animals may have different geometries and, consequently, may have different extracellular fractions and tortuosities. Even in the same animal, different regions may have different volume fractions. For example, the measurements for the gray matter of the somatosensory neocortex and subcortical white matter of the adult rat by Lehmenkühler et al. [46] show that the volume fraction of layer II, III, IV, and white matter are 0.19±0.002, 0.20±0.004, 0.21±0.003, and 0.23±0.007, respectively.

Actually, in [46], Lehmenkühler et al. determined the ECS volume fraction $\alpha$, tortuosity $\lambda$ and the non-specific uptake $k$ of TMA for the gray matter of the somatosensory neocortex and subcortical white matter of the rat during postnatal development. The extracellular volume fraction was largest in the newborn rats and diminished with age. In
white matter, for example, the earliest decrease in volume fraction was found at postnatal days 10-11; a further dramatic reduction occurred between postnatal days 10-21; there was no further decrease between postnatal day 21 and adults. The values of tortuosity ranged from 1.51 to 1.65. The variation of tortuosity was not significant at any age. Since the large extracellular volume fraction of the neonatal brain could significantly dilute ions, metabolites, and neuroactive substances released from cells, relative to release in adults, they concluded that the large volume fraction in young animals may be a factor in preventing anoxia, seizure, and spreading depression.

In 1996, volume fraction, tortuosity, and non-specific uptake also were studied during postnatal development after X-irradiation by Sykova et al. [77]. X-irradiation with a single dose of 40 or 20 Gy resulted in typical morphological changes in the tissue, namely cell death, extensive neuronal loss, blood-brain barrier damage. X-irradiation blocked the normal pattern of volume fraction decrease during postnatal development, and in fact brought about a significant increase. At postnatal days 4-5, $\alpha$ increased to 0.48±0.025 in the white matter. The large increase in volume fraction persisted for three weeks after X-irradiation. Tortuosity and non-specific uptake decreased significantly at postnatal days 2-5.

Many brain regions appear to be homogeneous and isotropic, but some regions of brain had been inferred from magnetic resonance imaging (MRI) to have structural anisotropy. In 1993, Rice et al. [67] studied anisotropic and heterogeneous diffusion in the turtle cerebellum. Measurements of the extracellular diffusion properties were made in three orthogonal axes of the molecular and granular layers of the isolated turtle cerebellum. Diffusion in the ECS of the molecular layer was anisotropic, that is, there were different values of the tortuosity factor $\lambda_i$, associated with each axis of that layer. The $x$- and $y$-axes lay in the plane parallel to the pial surface of this cerebellum with the $x$-axis in the direction of the parallel fibers. The $z$-axis was perpendicular to this plane. The tortuosity
values were $\lambda_x = 1.44 \pm 0.01$, $\lambda_y = 1.95 \pm 0.02$, and $\lambda_z = 1.58 \pm 0.01$. In contrast, the granular layer was isotropic with a single tortuosity value $\lambda_{Gr} = 1.77 \pm 0.01$.

Recently, measurements of extracellular volume fraction and water content were combined by Nicholson’s group [42] to show that hypotonic solutions cause water to move from the ECS to the ICS, while hypertonic solutions cause water to move from the ICS to ECS with only relatively small changes in total water in both cases. The extracellular volume fraction and tortuosity of the granular layer of the turtle cerebellum were determined. The volume fraction was 0.22 in normal saline, 0.12 in hypotonic medium, and 0.60 in the most hypertonic medium. Tortuosity was 1.70 in normal saline, 1.79 in hypotonic medium, and 1.50 in the most hypertonic saline. The extra- and intracellular space volumes show much larger changes than either total tissue volume or tortuosity.
Chapter 3

Lattice Gas Cellular Automata Method and Lattice Boltzmann Equation

In modeling real (physical or biological) systems, one might first derive partial differential (or more generally, mathematical) equations for the systems when it is possible. Then one solves the equations either analytically or numerically. For many interesting systems, the equations are nonlinear ones and analytic solutions are rarely available. Hence, numerical solutions become necessary. To get the numerical solution of the system, one may first discretize the continuum system using a technique such as a finite element method or finite difference technique, then solve the discretized system by computer.

In the description using partial differential equations, the underlying physical systems are viewed as a continuum, and the underlying variables in the equations are on a macroscopic level, whereas the variables in the discretized equation system are on a "microscopic" level. In fact, some real system could be genuinely discrete on the "microscopic" level, and in many cases, the continuous mathematical equations on the macroscopic level come from the discrete "microscopic" scale equation system as a limit by letting the "microscopic" scale become as small as possible. As computers get more powerful and better at handling these discrete "microscopic" equation systems, one might get the solution directly from this "microworld" by building discrete "microscopic" model systems.

The lattice gas cellular automata method or the related lattice Boltzmann equation [15], [16] as applied in hydrodynamics is one such example. The basic idea in using the lattice gas automata in hydrodynamics is to study the macroscopic evolution of a fluid using the simple microscopic level model for the fluid particles that can on a collective,
macroscopic scale mimic the behavior of the real fluid.

Although the idea of using discrete methods for modeling partial differential equations occurred very early, the first totally discrete model, a lattice gas automaton in a two-dimensional square lattice space, was proposed by Hardy, Pomeau, and de Pazzis in 1972 [28], [29]; now it is usually called the HPP model. The HPP model is pretty simple and deterministic—the evolution is reversible, but the Navier-Stokes equation derived from the model is anisotropic because the stress tensor lacks the necessary symmetry due to the square lattice geometry [82].

In 1986 [20], Frisch, Hasslacher, and Pomeau (FHP) proposed a lattice gas model, now well-known as the FHP model [21], based on a triangular lattice structure. This triangular lattice structure can guarantee an isotropic (at least to the order of their approximation) Navier-Stokes equation derived from the model. In their paper, the statement that cellular automata techniques can approximate the solutions of hydrodynamic partial differential equations was made. Now let me give a brief description of the FHP lattice gas model and the related lattice Boltzmann equation so that we can get more familiar with the idea of these methods.

3.1 FHP lattice gas model and the lattice Boltzmann equation

The FHP model is still quite similar to the HPP lattice gas automaton model. The FHP model is based on a regular two-dimensional triangular lattice as illustrated in Fig. 3.1. All particles have unit masses, move with unit velocity $c_i$ ($i = 1, \ldots, 6$) in one of the six possible directions of the lattice, each node $r$ has six links, the length of the link is the unit $|c_i|$ ($i = 1, \ldots, 6$), all particles are assumed to be located at some nodes $r$ at each integer time step $\tau$. The occupancy variable $n_i(r, \tau)$ is a function of position $r$ and time $\tau$ and subject to an exclusion principle, i.e., at a given time, at most one particle can lie
on each directed link; More exactly, if there is a particle moving with velocity \( c_i \) at the position \( r \) at time \( \tau \), \( n_i(r, \tau) \) is one, otherwise, it is zero. Also it is assumed that there is no resting particle at each node; Thus at each node the maximum number of particles is six, therefore the FHP model is also called the six-particle (bit) FHP model.

The evolution of the automata proceeds with two successive steps: collision followed with propagation. Collision operator \( C \): At each node \( r \), particles collide, then propagate. During collision, a particle’s direction changes according to some collision rules. Propagation operator \( S \): Particles move one unit in one of six possible directions during one unit time. \( S \) also is called the streaming operator.

Thus the entire evolution, \( S \cdot C \), of the automata is

\[
n_i(r + c_i, \tau + 1) = n_i(r, \tau) + \Delta_i(\{n_j(r, \tau)\})
\]

where \( \Delta_i(\{n_j(r, \tau)\}) \) is the collision function, which depends on the collision rules specified. This is the lattice gas microdynamical equation.

For the FHP model, the collision rules are illustrated in Fig. 3.2. In the left column are the incoming states, and the middle column are outgoing states after colliding, the
Figure 3.2: The collision rules for the FHP lattice gas automaton model. In the left column are input states, in the middle are output states, and in the right are transition probabilities.
right column are the transition probabilities. Collisions must preserve number and momentum. The first row is the two-body head-on collision. Only two particles coming from opposite directions can collide and scatter by randomly rotating $\pi/3$ either clockwise or counter-clockwise. The second row is a three-body collision. Three particles which are $2\pi/3$ apart from each other scatter by rotating $\pi/3$, while three particles with one pair of head-on particles change to only one possible configuration. Fig. 3.2 states all possible configuration changes after collision, except those degeneracies by sixfold rotational symmetry of the triangular lattice space or by mirror reflections.

With these collision rules, the collision function $\Delta_i(\{n_j(r, \tau)\})$ of the FHP 6-bit lattice gas model is

$$
\Delta_i(\{n_j\}) = \xi_{\tau,r} n_{i+1} n_{i+4} \bar{n}_i \bar{n}_{i+2} \bar{n}_{i+3} \bar{n}_{i+5} \\
+ (1 - \xi_{\tau,r}) n_{i+2} n_{i+5} \bar{n}_i \bar{n}_{i+1} \bar{n}_{i+3} \bar{n}_{i+4} \\
- n_i n_{i+3} \bar{n}_{i+1} \bar{n}_{i+2} \bar{n}_{i+4} \bar{n}_{i+5} + n_{i+1} n_{i+3} n_{i+5} \bar{n}_i \bar{n}_{i+2} \bar{n}_{i+4} \\
- n_i n_{i+2} n_{i+4} \bar{n}_{i+1} \bar{n}_{i+3} \bar{n}_{i+5}.
$$

Here, $\bar{n}_i = 1 - n_i$, $\xi_{\tau,r}$ denotes a time- and node-dependent Boolean random variable which takes the value one when head-on colliding particles are to be rotated counter-clockwise and zero otherwise. In the above and following equations, the index (modulo 6) is always used.

Obviously the collision rules conserve the mass and momentum. Mass conservation and momentum conservation can mathematically be expressed as

$$
\sum_i n_i(r + c_i, \tau + 1) = \sum_i n_i(r, \tau),
$$

(3.3)

$$
\sum_i c_i n_i(r + c_i, \tau + 1) = \sum_i c_i n_i(r, \tau).
$$

(3.4)

Since the occupancy variable $n_i$ in the lattice gas microdynamical equation is either one or zero, it can be noisy. To avoid this, one can use its average $N_i = E(n_i)$ where the
brackets denote the ensemble average (for details, see [21]), $N_i(\mathbf{r}, \tau)$ gives the probability of finding a particle with velocity $\mathbf{c}_i$ at position $\mathbf{r}$ and time $\tau$ and ranges between 0 and 1, rather than equaling only 0 and 1 as in the case of $n_i$.

From applying this average to the microdynamical equation, it follows that

$$N_i(\mathbf{r} + \mathbf{c}_i, \tau + 1) - N_i(\mathbf{r}, \tau) = E(\Delta_i(\{n_j\})),$$

Thus one obtains the discrete Boltzmann equation

$$N_i(\mathbf{r} + \mathbf{c}_i, \tau + 1) - N_i(\mathbf{r}, \tau) = \Delta_i(\{N_j\})$$

by letting $\Delta_i(\{N_j\})$ approximate $E(\Delta_i(\{n_j\}))$. Here the collision operator is given by

$$\Delta_i(\{N_j\}) = \frac{1}{2} N_{i+1} N_{i+4} N_{i+2} N_{i+3} N_{i+5}$$

$$+ \frac{1}{2} N_{i+2} N_{i+5} N_{i+1} N_{i+3} N_{i+4}$$

$$- N_i N_{i+3} N_{i+1} N_{i+2} N_{i+4} N_{i+5} + N_{i+1} N_{i+3} N_{i+5} N_i N_{i+2} N_{i+4}$$

$$- N_i N_{i+2} N_{i+4} N_{i+1} N_{i+3} N_{i+5}.$$

The approximation $E(\Delta_i(\{n_j\})) \approx \Delta_i(\{N_j\})$ requires the assumption that particles coming into a collision are uncorrelated. This assumption is usually not true, especially when the particle density is very high, but the approximation holds well if the particle density is low. The validity of this assumption for a lattice gas has been explored by Boghosian [8].

A macroscopic variable density is introduced by

$$\rho(\mathbf{r}, \tau) = \sum_i N_i(\mathbf{r}, \tau),$$

the mass current is defined as

$$\mathbf{j}(\mathbf{r}, \tau) = \sum_i \mathbf{c}_i N_i(\mathbf{r}, \tau),$$
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and the mean velocity $\mathbf{u}$ is

$$\mathbf{u}(\mathbf{r}, \tau) = \frac{j(\mathbf{r}, \tau)}{\rho(\mathbf{r}, \tau)}.$$ 

Locally, for a given $\rho$ and $\mathbf{u}$, the $N_i$'s can be computed from both $\rho$ and $\mathbf{u}$ at the equilibrium (with the assumption $\mathbf{u}$ is small) and the Boltzmann equation by a Fermi-Dirac distribution

$$N_i = \{1 + \exp(h(\rho, \mathbf{u}) + q(\rho, \mathbf{u} \cdot \mathbf{c}_i))\}^{-1}$$

where $h$ and $q$ satisfy equations with no simple solutions. However, when $\mathbf{u} = 0$, $N_i = \rho/6$, and $h$ and $q$ can be expanded in a Taylor series around $\mathbf{u} = 0$, the result can be used to compute mass and momentum flux to leading order in the macroscopic gradients. Second-order terms are obtained by a Chapman-Enskog expansion. Thus the hydrodynamic equations can be obtained:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{u}) = 0 \quad (3.7)$$

and

$$\frac{\partial}{\partial t}(\rho u_\alpha) + \sum_\beta \frac{\partial}{\partial r_\beta} [g(\rho)\rho u_\alpha u_\beta]$$

$$= -\frac{\partial}{\partial r_\alpha} P + \eta_1(\rho)\nabla^2 u_\alpha + \eta_2(\rho) \frac{\partial}{\partial r_\alpha} \nabla \cdot \mathbf{u} \quad (3.8)$$

with $g(\rho) = (\rho - 3)/(\rho - 6)$, $P = \rho/2$, and $\eta_1(\rho), \eta_2(\rho)$ are the shear and bulk viscosities. Where the $\alpha$ and the $\beta$ are either $x$ or $y$.

Equation (3.7) is the usual continuity equation, which expresses the conservation of mass, and (3.8) is in the form of the Navier-Stokes equation, which comes from the momentum conservation equation.

The invention of the FHP model has stimulated research on lattice gas automata. Until now, the lattice gas automata and the corresponding lattice Boltzmann equations, have been successfully applied to many fields such as single or multi-phase fluids (porous
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media) [10], [26], [27], [69], phase transition phenomena [2], [3], and chemical reaction-diffusion systems [14], [30], [35], [36], [37], [43]. The lattice gas automata and the lattice Boltzmann equations also can be used as numerical schemes to “solve” partial differential equations, such as the Navier-Stokes equation [20], Burger’s equation [8], the wave equation [9], and reaction diffusion equations [13], [64].

The FHP model possesses some shortcomings. One problem is that at most one particle is allowed in each direction at a given time. Another problem is that the results from the LCA tend to be very noisy, with significant density and velocity fluctuations occurring. However, the later shortcoming can be overcome by their floating-point-number variation—the method of the lattice Boltzmann equations.

3.2 Migration of ions in the brain as a porous medium

Chen et al. [10] and Rothman [69] studied the fluid flow through porous media by using the lattice gas cellular automata method where only a simple no-slip boundary condition at the interphase was used. Our ultimate aim here is, of course, to build a lattice gas cellular automata model so that a more complicated transport boundary condition at the membrane can be taken into account. To begin, we will consider a simple case when the substance cannot cross the membrane, i.e., the zero-flux membrane condition, and now, we try to perform several preliminary simulations using the FHP model for this case.

First, we have to set up a suitable two-dimensional porous medium which is going to be studied. We can do this because as the lattice link unit becomes smaller, the pore-space can approximate any kind of two-dimensional geometry. The volume fraction, usually called the porosity in a porous medium, was defined by Rothman [69] as the number of lattice nodes in the pore space divided by the total number of lattice nodes. To match the zero-flux membrane boundary condition, we adopt the no-slip boundary
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condition \((u = 0)\) at the membrane wall.

In their experiments, Nicholson and Phillips [57] used an iontophoresis circuit to eject ions from a micropipette into the brain-cell microenvironment. To match these experiments on brain tissue, we need to continually inject particles (ions) for some time duration at a point, say at a node \(A\). If we use only one node \(A\) to inject particles, at most six particles can leave node \(A\) at each time step without violating the exclusion principle, thus even many time steps later, there are still very few particles on the lattice. To have more particles on the lattice within a short time, we use the six neighbors of the node \(A\) to inject particles. For the first several time steps, we can put 36 particles on the lattice, then 18 particles. For the following two numerical experiments, after three thousand time steps, only 10 particles can be put on the lattice without violating the exclusion principle.

In this situation, we may introduce the discrete density \(C(r, \tau)\) at each node \(r\) at time \(\tau\) as

\[
C(r, \tau) = \sum_i n_i(r, \tau),
\]

the mass current as

\[
J(r, \tau) = \sum_i c_i n_i(r, \tau),
\]

and the discrete mean velocity \(v\) as

\[
v(r, \tau) = \frac{J(r, \tau)}{C(r, \tau)}.
\]

Numerical experiments are shown in Fig. 3.3 and Fig. 3.4. Here we use a time average and space average to reduce the microscopic noise which arose from the LCA model. Fig. 3.3 shows the velocity field of the ion flow in a porous medium at the 3000th time step. The porous medium has volume fraction 0.4411. The total number of nodes in the porous medium is \(301 \times 121\). The lattice has a 300 unit length in the \(x\) direction and a
Figure 3.3: Flow of ions through a porous medium. The light shaded regions represent impermeable material, i.e., the solid space. The whole medium measures 300 nodes in the $x$-direction and 120 nodes in the $y$ direction. Until the 3000th time step, the number of particles injected is 34568. The central node of the porous medium is the position where particles are injected.
120 \times \sqrt{3}/2 unit length in the y direction. Each vector points in the direction of local flow and the length of each vector is proportional to flow speed. The vectors were obtained by averaging over 8\times6 nodes on the lattice and over time steps 2000 to 3000. All of those nodes on y = 0 and y = 120 \times \sqrt{3}/2 are chosen to be in the solid space. When particles hit the boundary, they bounce back, the average velocity is 0. Once particles reach those nodes in the pore space on the boundary x = 0 and x = 300, they will move away and never come back. So for these nodes, the density is always 0.

Fig. 3.4 is the ion flow of a chosen porous medium at the 4000th time step. The total number of nodes of the porous medium is 161\times161. Its volume fraction is 0.3063. The vectors are obtained by averaging from the 2000th time step to the 4000th time step and over its 8\times6 neighborhood nodes.

In experiments on brain tissue [55] [57], [76], researchers usually inject ions at a constant rate. To have such a constant injection rate, we need to place particles on the injection node in the direction, say \(c\); at a constant rate. However, it is possible that at the node A, there has been a particle moving in direction \(c\); thus, after the injection operation, in that direction, there will be two particles which will violate the exclusion principle, at most one particle is allowed in a direction. Using the FHP model, the constant injection rate cannot be achieved without violating the exclusion principle. It is these real experiments on brain tissue that force us not to use the FHP model and make our model for the ion diffusion in brain different from Rothman’s [69] and Chen’s [10]. We will build models such that the exclusion principle is not required.

These two porous media on which we performed numerical experiments are set up artificially. We have not incorporated the structure of the brain into them, at least the volume fractions are not those values obtained from various brain tissues. The average ECS spacing between cell membranes in the mammalian brain is in the range 0.01-0.04
Figure 3.4: The velocity field of the ion flow through a porous medium. The shaded regions is the solid space. The volume fraction is 0.3063. The porous medium measures 160 unit length by 160 unit length. Until the 4000th time step, 58666 particles have been injected. The centre node is still the position where particles are injected.
\( \mu m \), while diameters of cellular elements range from 0.1 to 50 \( \mu m \). Their ratio is between \( 2 \times 10^{-4} \) and 0.4. If we choose \( d = 0.04 \mu m \) and \( l = 6 \mu m \), the ratio \( d/l \) is \( 2/3 \times 10^{-2} \). If we use the lattice gas cellular automata model, to have particles fully collide in the pore space, Rothman [69] stated that the width of the pore space needs at least 12 lattice links.

To construct a medium which represents the brain tissue reasonably, if we let the width of the ECS to have 10 lattice links across, then we have to choose a 1500 \( \times \) 1500 lattice size so that the medium has one cell. If we want to study the migrations of substances in brain, we need to deal with groups of cells; thus, the lattice size will dramatically increase. For example, dealing with 10 \( \times \) 10 cells requires us to use 15000 \( \times \) 15000 lattice size. However, due to our limited computer resources, we are unable to perform simulations for a medium with such a large lattice size to make the simulations more realistic. Thus, we may have to use the lattice Boltzmann equation instead of the lattice gas cellular automata.

The boundary condition used in the above numerical experiments is the “bounce back” condition, i.e., when a particle hits a boundary node, it will bounce back. This boundary condition is not realistic since the particle also could be reflected. Our problem here is the diffusion with complicated membrane boundary geometries and membrane boundary conditions. Dealing with the diffusion phenomena, the square lattice should be good enough [35], [36], [37], [43]. Using the square lattice, the bounce-back is the reflection; thus, the problem which arises from the reflection using triangle lattice can be avoided. Compared to the triangular lattice, the square lattice is easier to handle, and the computation time will be shorter.

The boundary condition used for the membrane is the zero-flux condition. When we study the movements of substances such as potassium, the membrane boundary conditions are very complicated. Three factors, membrane potential, concentration differences, and permeability, jointly determine the flow of a particular ion across the membrane. The
magnitude and direction of the net transfer of a given ionic species must reflect the influences of these three factors.

In fact, the most important and crucial difficulty here is how to incorporate the membrane properties \((\text{membrane conditions})\) together with the complicated geometries into the system, such as how to put the concentration difference, potential difference across the membrane into the model, and how to set up the medium such that the medium captures the geometrical effects of brain tissue on the ion movement. Also it must be decided how to let the specific particles pass through the membrane channel along the chosen lattice connection, and so on.

When a particle hits the membrane wall at some boundary node, it could pass through the membrane as well as bounce back. To make the problem simple, we can assume that the probability of particles which can pass through the membrane at each node is the same for every particle at that node. However, we need to determine how the probability is related to the membrane potential, concentration difference, and permeability. To overcome these difficulties and to model the ion movement using the LCA and the LBE are the objective of the rest of this thesis.
Chapter 4

A Lattice Cellular Automata Model for Ion Diffusion in the Brain-Cell Microenvironment and Determination of Tortuosity and Volume Fraction

4.1 Introduction

Understanding diffusion is important for many vital processes in brain. Substances such as TMA or TEA move through the brain-cell microenvironment almost entirely by diffusion when there is no external applied electrical effects. In this chapter, we will study the diffusion process of substance such as TMA or TEA within the brain-cell microenvironment.

The concentration of substances within the brain-cell microenvironment is not continuous over the whole space. To avoid these discontinuities, in 1981, Nicholson and Phillips [57] used the averaging theory to derive the effective diffusion equation (2.19) for the diffusion of TMA or TEA. Equation (2.19) successfully reduces the problem in a complicated geometry for the brain as a porous medium to a diffusion problem in a simple medium with the geometries of the brain incorporated into the model. Thus, studying diffusion in the brain-cell microenvironment is equivalent to that in a simple medium with an effective diffusion coefficient \( D_e \equiv D/\lambda^2 \) and with an altered source term \(< q >/\alpha\).

The effective diffusion coefficient \( D_e \) is affected by the pore structure, i.e., when the tissue is viewed as a continuum, the effective diffusion coefficient is obtained by averaging over many cells. The tortuosity formally may be defined as \( \lambda = \sqrt{D/D_e} \). The tortuosity
incorporates the brain structure and is affected by the structure. It is a lumped parameter that is dependent on such geometrical properties as connectivity and pore size, so it should be directly related to the geometry of the porous medium. However, the effects of these geometrical properties on the tortuosity remain unknown, and unveiling such relationships is one of the objectives of the research in this chapter.

The ion-selective microelectrode permits the direct examination of ion diffusion in the brain and monitoring the ionic concentration in real time at a specific point in a given tissue. Thus, by fitting the experimental data to a solution of the effective diffusion equation (2.19) at two different times, the parameters $\lambda$ and $\alpha$ can be computed [57]. However, it is difficult to use experimental data from the brain to study how the brain geometrical properties such as connectivity and pore size affect the tortuosity and the volume fraction because the cellular geometry in each particular area of the brain is fixed and is usually not known exactly. Since the experimental data coupled with porous media theory are inadequate to resolve these additional issues, we seek an alternative theoretical model to achieve this.

In 1993, El-Kareh et al. [18] constructed a theoretical model for tumors and studied the effects of cell arrangement and volume fraction on the effective diffusion coefficient (diffusivity) $D_e$. They found that the shapes and arrangement of the cells had little influence on the effective diffusion coefficient and, in turn, on the tortuosity. However, their study contained only a few regular cell shapes and periodic cell arrangements.

In this chapter, to mimic the experimental situation in the brain, we first build a microscopic level discrete model, i.e., the lattice cellular automata (LCA) model [15], [16], for diffusion of ions within the brain-cell microenvironment. Then, as an application of the model, we study how the geometrical properties of the medium such as connectivity and pore size affect the tortuosity and the volume fraction.

Both the tortuosity $\lambda$ and the volume fraction $\alpha$ are geometrical factors. In the
derivation of these parameters [57], they are treated as independent quantities, but, intuitively, it seems that some constraints between them would occur. Nicholson and Rice [58], [59] proposed that a relationship between the tortuosity and volume fraction, i.e., Archie's Law,

\[ \lambda^2 = \alpha^{-\beta} \]  

where \( \beta \) is a constant between 1/2 and 2/3, may be true. We can use our results to test whether Archie's law is true for various porous media. Such a test is difficult to achieve from experimental data because the geometrical structure of the brain is unknown and cannot be changed arbitrarily.

In Section 4.2, we present an LCA model and the corresponding LBE for diffusion in the brain-cell microenvironment. The choices of additional conditions, such as the membrane boundary condition, to match the assumptions, and how we do the numerical experiments are given in Section 4.3. In Section 4.4, we describe how the computations of the tortuosity and the volume fraction are performed. In Sections 4.5 and 4.6, we present how we generate two- and three-dimensional porous media and the corresponding numerical results. Finally, we conclude with a discussion of the method developed here and the results.

4.2 Lattice cellular automata model

The problem of interest here is diffusion in a complicated geometry, so we can use the ideas developed by Chopard and Droz [11] and by Kapral and his group [35]–[43]. We intend to perform numerical simulations in both two and three dimensions. The LCA models for two and three dimensions can be built similarly. Here we choose to present how we build the three-dimensional LCA model since the two-dimensional model can be modified from the three-dimensional case easier than the other way around. For
simplicity, we choose a cubic lattice $\mathcal{L}$, which is much easier to handle than the pseudo-four-dimensional, face-centered-hypercubic model \cite{21} and is generally sufficient to solve diffusion problems.

We assume that all particles have unit masses, move on the cubic lattice $\mathcal{L}$, and update on the lattice. Each node of the lattice is labeled by the discrete vector $\mathbf{r} = (x, y, z)$ (see Fig. 4.1), and each particle is associated with discrete directional length vectors $\mathbf{c}_i$, $i = 1, 2, 3, 4, 5, 6$, which point in one of six possible directions on the lattice. The $\mathbf{c}_i$ are vectors connecting the node to its nearest neighbors where $i = 1, 2, 3$ correspond to the directions along the positive $x$, $y$, $z$ axes, respectively; more specifically, $\mathbf{c}_1 = \varepsilon(1, 0, 0)$, $\mathbf{c}_2 = \varepsilon(0, 1, 0)$, $\mathbf{c}_3 = \varepsilon(0, 0, 1)$ where $\varepsilon$ is the lattice link length. The other three directions are defined according to the relation

$$c_{i+3} = -c_i, \quad i = 1, 2, 3.$$  

Let $\mathcal{S}$ be the set of all vectors $\mathbf{s} = (s_1, s_2, s_3, s_4, s_5, s_6)$ such that $s_i$ is a nonnegative integer. A configuration of particles at node $\mathbf{r}$ at time $t$ can be described by a vector $\mathbf{n}(\mathbf{r}, t) = (n_1, n_2, n_3, n_4, n_5, n_6)(\mathbf{r}, t)$ with values in the state space $\mathcal{S}$. The value $n_i(\mathbf{r}, t) = $
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$m \geq 0$ indicates there are $m$ particles at the node $\mathbf{r}$ at time $t$ moving in the direction $\mathbf{c}_i$.

A configuration $\mathbf{n}_L(t)$ of the lattice $L$ at time $t$ is described by a field

$$
\mathbf{n}_L(t) = \{n(\mathbf{r},t) : \mathbf{r} \in L, n \in S\}.
$$

The evolution of this LCA model is a sequential change of configuration $\mathbf{n}_L(t)$ of the lattice at discrete time steps $t = 0, \tau, 2\tau, \ldots$. For each configuration change, our model proceeds with three successive steps at each node: particle injection, particle rotation (or collision), and propagation.

Injection operator $I$: During the particle injection step, substances (or drugs) are placed at some node on the lattice. We define the injection operation as

$$
I_i: n_i(\mathbf{r}, \cdot) \rightarrow n_i(\mathbf{r}, \cdot) + q_i(\mathbf{r}, \cdot) \quad (4.2)
$$

where $q_i$ represents the amount of the substance injected and $q_i/\tau$ is the injection rate of this substance per unit time step $\tau$ at node $\mathbf{r}$ at the time $t$ that is moving in the direction $i$.

In their experiments, Nicholson and Phillips [57] used a constant current iontophoresis circuit to eject ions from a micropipette into the brain-cell microenvironment. The particle injection step tries to mimic this experimental situation. For this particular application, a constant injection amount $q_i$ of the substance for some time period will suffice. Without loss of generality, we always choose a node near the center of the lattice $L$ as the position where substances are injected, provided this coincides with an extracellular point.

Rotation (collision) operator $R$: At each node $\mathbf{r}$, each incoming particle has six possible directions along which to leave. The result of an operation $R_i$, $i = 1, \ldots, 6$, is to deflect the particle entering in the direction $\mathbf{c}_k$ into the direction $\mathbf{c}_{i+k}$, $k = 1, \ldots, 6$. During this step, the rotation operator $R$ picks out an angle specified by one of the $R_i$,.
and all particles entering a node rotate by this angle. These rotations are performed independently for each node on the lattice $L$. Mass is conserved at each node, but momentum is not. We assume that the probabilities associated with these rotations $R_i$ are $p_i$, $i = 1, \ldots, 6$, respectively, and these probabilities are subject to the normalization condition

$$p_1 + p_2 + p_3 + p_4 + p_5 + p_6 = 1.$$  

To explicitly construct the rotation operator, we let $\xi_i(r, t), r \in L, t = \tau, 2\tau, \ldots$, be independent sequences of identically distributed, independent, Bernoulli-type random variables, i.e., $\xi_i$ is either 1 or 0, satisfying

$$\xi_1 + \xi_2 + \xi_3 + \xi_4 + \xi_5 + \xi_6 = 1,$$

and the probability that the $i$th variable $\xi_i$ is one is $p_i$. Using these variables, we then can write the rotation operator $R$ as

$$R_i : n_i \rightarrow n_i^C = \sum_{j=1}^{6} \xi_j n_{i+j}$$

$$= n_i + \sum_{j=1}^{6} \xi_j (-n_i + n_{i+j})$$

$$\equiv n_i + \Delta_i^C(n)$$

(4.3)

where $\Delta_i^C(n)$ is the collision function. It is understood that the index is modulo 6.

Propagation operator $S$: After particles rotate, then they propagate. In this propagation step, each particle moves from its present node $r$ in the direction $c_i$ to its nearest-neighbor node $r + c_i$. The propagation can be expressed as

$$S_i : n_i(r, t) \rightarrow n_i(r + c_i, t + \tau), \ i = 1, 2, \ldots, 6;$$

$S$ also is called the streaming operator. Note that only the propagation operation consumes a unit of time $\tau$. 


Thus each configuration change, $S \cdot R \cdot I$, of the automata is

$$n_i(r + c_i, t + \tau) = n_i(r, t) + q_i(r, t) + \Delta_i((n + q)(r, t))$$

$$= \sum_{j=1}^{6} \xi_j n_{i+j}(r, t) + \sum_{j=1}^{6} \xi_j q_{i+j}(r, t). \quad (4.4)$$

This is the lattice gas microdynamical equation; it is fully discrete in space, time, and concentration. The propagation and rotation operations are intended to describe the free streaming and collisions that occur in the intra- and extracellular spaces; their net effect is the diffusion phenomenon.

The occupancy variable $n_i$ in the lattice gas microdynamical equation is either a positive integer or zero; it can be noisy when interpreting the results of a computation. To avoid this noise, one can use its average $N_i = E(n_i)$ where $E$ denotes the average. We take the average of the microdynamical equation (4.4). Since the Bernoulli-type random variables $\xi_i$ are independent of the occupation numbers $n_i$ and the injection amount $q_i$, it follows that

$$N_i(r + c_i, t + \tau) = \sum_{j=1}^{6} p_j N_{i+j}(r, t) + \sum_{j=1}^{6} p_j Q_{i+j}(r, t) \quad (4.5)$$

where $Q_i$ is the average of the source $q_i$, i.e., $Q_i = E(q_i)$. Equation (4.5) is the lattice Boltzmann equation (LBE) associated with our system.

Introduce a variable density by

$$C(r, t) = \sum_{i=1}^{6} N_i(r, t).$$

For our application, we will assume that all particles entering a node will rotate according to $R_i$ with equal probability, i.e.,

$$p_1 = p_2 = p_3 = p_4 = p_5 = p_6 = 1/6.$$ 

Thus, we can rewrite the LBE (4.5) as

$$N_i(r, t + \tau) = \frac{1}{6} \sum_{j=1}^{6} N_{i+j}(r - c_i, t) + \frac{1}{6} \sum_{j=1}^{6} Q_{i+j}(r - c_i, t).$$
Summing over $i$, we have

$$C(r, t + \tau) = \frac{1}{6} \sum_{i=1}^{6} C(r - c_i, t) + \frac{1}{6} \sum_{i=1}^{6} \sum_{j=1}^{6} Q_{i+j}(r - c_i, t). \quad (4.6)$$

Taylor expanding $C(r - c_i, t)$, $C(r, t + \tau)$ about $(r, t)$, we obtain

$$C(r - c_i, t) = C(r, t) - c_i \cdot \nabla C(r, t)$$

$$+ \frac{1}{2} \nabla \cdot ((c_i \cdot \nabla C)c_i)(r, t) + h(C, c_i)(r, t) + O(\varepsilon^4), \quad (4.7)$$

$$C(r, t + \tau) = C(r, t) + \tau \frac{\partial C}{\partial t}(r, t) + O(\tau^2) \quad (4.8)$$

where $h(C, c_i)$ is a function determined by a third-order Taylor expansion, and $\varepsilon$ is the lattice link length.

Furthermore, we assume that $\tau$ is of order $\varepsilon^2$ and let the diffusion coefficient be given by

$$D = \frac{1}{6\varepsilon^2} \quad (4.9)$$

Taking the approximation in (4.7), (4.8) to second order in $\varepsilon$, from (4.6), we can get the diffusion equation

$$\frac{\partial C}{\partial t}(r, t) = D \nabla^2 C(r, t) + f(r, t) \quad (4.10)$$

where the source term is defined by

$$f(r, t) = \lim_{\varepsilon \to 0} \frac{6D}{\varepsilon^2} \sum_{i=1}^{6} Q_i(r, t). \quad (4.11)$$

Derivation of the diffusion equation (4.10) implies that the microdynamical equation (4.4) and the microscopic dynamical LBE (4.5) do describe the diffusion phenomenon within the pore space on the continuous macroscopic level. The LBE (4.5) is discrete in time and space; whereas it is continuous in the density variable. It can be related

---

It seems that the limits in (4.11) and in (4.12) do not exist; however, with our choices of the injection amount $Q_i$ in the next section, the function $f$ is related to the Dirac delta function.
to a finite-difference scheme for a continuous equation. In fact, (4.6) is related to the forward-time central-space finite-difference scheme [78] for Equation (4.10).

The two-dimensional LCA model can be built in exactly the same way as for the three-dimensional case except there are several dimension-related changes. For example, we use a square lattice rather than a cubic lattice. The discrete direction length vectors are \( c_i = \varepsilon \left( \cos((i - 1)\pi/2), \sin((i - 1)\pi/2) \right), \) \( i = 1, 2, 3, 4, \) and the two-dimensional LBE has the form

\[
N_i (r + c_i, t + \tau) = \sum_{j=1}^{4} p_j N_{i+j} (r, t) + \sum_{j=1}^{4} p_j \mathcal{Q}_{i+j} (r, t).
\]

The diffusion coefficient is given by \( D = \varepsilon^2/(4\tau) \), and the corresponding source term is given by

\[
f(r, t) = \lim_{\varepsilon \to 0} \frac{4D}{\varepsilon^2} \sum_{i=1}^{4} \mathcal{Q}_i (r, t).
\] (4.12)

### 4.3 Numerical procedures and membrane boundary condition

Since the lattice gas microdynamical equation (4.4) results in noisy solutions when it is applied to diffusion within the ECS of the brain, instead we will use the LBE (4.5) to perform the simulations. Like the microdynamical equation (4.4), the LBE also can be split into three steps, i.e., particle injection, rotation, and propagation. During the particle injection and rotation steps, a boundary condition can be implemented by choosing a suitable collision rule at the boundary node. Since these two operations occur locally and do not depend on other nodes, the geometry of the membrane boundary is not important. Thus, the LBE is capable of efficiently handling complicated boundary geometries, which are difficult to incorporate when using conventional numerical methods such as the finite-difference scheme (4.6).

Using the LCA model to perform numerical simulations, we first set up the brain as a porous medium. Since the brain is three dimensional, we focus on the procedures
in three dimensions, but we indicate the alterations necessary for the two-dimensional computations. The pore space of the porous medium can approximate any kind of brain geometry by choosing the lattice link length $\varepsilon$ to be sufficiently small. To construct a porous medium, it is necessary to use an integer variable to represent whether the node is in extracellular (void) or in intracellular (solid) space, or is at the membrane. The membrane of each cell always is chosen to be along the lattice links connecting the nearest membrane nodes, so the membrane forms a closed surface which separates the ICS from the ECS. Each node on the membrane is called a membrane boundary node, whereas the ECS node with at least one link connected to a membrane boundary node is an ECS boundary node.

Fig. 4.2 is an example of a two-dimensional porous medium we generated. The shaded regions in Fig. 4.2 represent "solid" space, and the remaining regions are in the pore space.

Rothman [69] defined the porosity\(^2\) of a porous medium as the number of lattice nodes in the pore space divided by the total number of lattice nodes. Here we need a more precise definition, so half of the membrane boundary nodes will be counted as

\(^2\)In [6], the definition of the porosity is the volume fraction, as we mentioned earlier.
being in the pore space. This definition of porosity corresponds to the ratio between the total volume of the pore space and the total volume of the medium. This is not the volume fraction, which is usually interpreted to be the same as the porosity, because the representative elementary volume $V$ is not necessarily the total volume of the medium [4]. Thus, the definition of the volume fraction $\alpha = V_0/V$ is not the same as that of the porosity, i.e., the volume fraction is a local quantity in the medium. The porosity does not vary with position, but the volume fraction can vary. Hence, we will call $\alpha$ the local volume fraction and the volume fraction of the medium will be referred to as the average value of the local volume fractions over all the pore space. In this chapter, we will treat the porosity and the volume fraction of a medium as distinct parameters.

When we generate various porous media for our numerical experiments (details are given in Sections 5 and 6), we always place the center of the lattice in the pore space, without loss of generality. To match Nicholson and Phillips’ experimental situation, we assume that particles are injected with a constant rate for some time period $T$ only at the center node $r = r_0$ of the lattice $\mathcal{L}$, i.e., $Q_i(r, t) = Q/6$ if $r = r_0$, $t \leq T$; $Q_i(r, t) = 0$ otherwise, $i = 1, \ldots, 6$. Thus, the source term (4.11) becomes

$$f(r, t) = \begin{cases} \lim_{\varepsilon \to 0} 6DQ \frac{1}{\varepsilon^3} & \text{if } r = r_0, \ t \leq T, \\ 0 & \text{otherwise.} \end{cases}$$

Let

$$d(r) = \begin{cases} \frac{1}{\varepsilon^3} & \text{if } r = r_0, \\ 0 & \text{otherwise.} \end{cases}$$

Then, $\int d(r) d^3x = 1$ because the volume of each basic cube associated with each node of the lattice $\mathcal{L}$ is $\varepsilon^3$. Thus, as $\varepsilon \to 0$, the function $d(r)$ tends to the Dirac delta function $\delta(r - r_0)$, but the mass $6D\varepsilon Q$ injected per unit time per unit volume also tends to 0. When we are performing the simulation, we cannot let $\varepsilon$ be 0. Therefore, for the
three-dimensional lattice, we have

\[ f(r, t) \approx 6D\varepsilon Q \delta(r - r_0)H(T - t) \]  

(4.13)

where \( H \) is the Heaviside step function.

For the two-dimensional lattice, we choose \( Q_i(r, t) = Q/4 \) if \( r = r_0, \ t \leq T; Q_i(r, t) = 0 \) otherwise, \( i = 1, \ldots, 4 \). In two-dimensions, the function

\[ d(r, t) = \begin{cases} \frac{1}{\varepsilon^2} & \text{if } r = r_0, \\ 0 & \text{otherwise} \end{cases} \]

tends to the two-dimensional Dirac delta function \( \delta(r - r_0) \) as \( \varepsilon \to 0 \). Thus, the source term (4.12) becomes

\[ f(r, t) = 4DQ\delta(r - r_0)H(T - t). \]  

(4.14)

Note that there is a very interesting difference between cases in two and three dimensions. Equation (4.13) for three dimensions is only an approximation, whereas (4.14) for two dimensions is an equality. There is a small parameter \( \varepsilon \) in (4.13) but not in (4.14).

To simulate the LBE (4.5), we need initial conditions and boundary conditions for the medium (the lattice \( \mathcal{L} \)). The initial condition \( N_i(r, 0) \) for the simulations is set equal to zero at each node of the lattice. Since this problem involves only diffusion in the ECS, we do not include any background density of ions as occurs in the experimental situation. We choose an absorbing boundary condition for the lattice \( \mathcal{L} \), i.e., once the particle reaches the boundary, it is absorbed and can no longer return to \( \mathcal{L} \). This is equivalent to setting the \( N_i(r, t) \) equal to zero.

In order to obtain the effective diffusion equation (2.19), it was assumed that ions cannot cross the membrane, which is equivalent to zero-flux of ions across the membrane. At the ECS boundary node \( r \), at least one of the nodes \( r + c_i, \ i = 1, \ldots, 6 \), is a membrane node. Thus, in using the LBE, the quantity \( N_j(r + c_i, t) \) at the membrane node \( r + c_i \)
may not be well-defined. To achieve a zero-flux condition, we can use a bounce-back membrane boundary condition, i.e., when a particle hits a membrane node, the particle will bounce back. In terms of the concentration variable $C$, this is represented for the case of one membrane node, say, $r + c_1$, as

$$C(r + c_1, t) = C(r, t). \quad (4.15)$$

Thus, the concentration at $r$ at time $t + \tau$ is given by

$$C(r, t + \tau) = \frac{1}{6} \sum_{i=2}^{6} C(r + c_i, t) + \frac{1}{6} C(r, t). \quad (4.16)$$

Taylor expanding (4.16) at node $r$ and at time $t$, we obtain at the ECS boundary node

$$C_x(r, t) = \left\{ \frac{1}{2} C_{xx} + C_{yy} + C_{zz} - \frac{C_t}{D} \right\} (r, t) \varepsilon + O(\varepsilon^2). \quad (4.17)$$

(Note the factor 1/2 in front of $C_{xx}$.)

Alternatively, to achieve a zero-flux condition, we could use a reflection condition (reflecting about the ECS boundary node $r$) given by

$$C(r + c_1, t) = C(r - c_1, t), \quad (4.18)$$

which implies that

$$C(r, t + \tau) = \frac{1}{6} \sum_{i=2}^{6} C(r + c_i, t) + \frac{1}{6} C(r - c_1, t).$$

Again using a Taylor expansion, we obtain

$$C_x(r, t) = \frac{1}{2} \left\{ C_{xx} + C_{yy} + C_{zz} - \frac{C_t}{D} \right\} (r, t) \varepsilon + O(\varepsilon^2). \quad (4.19)$$

Thus, at the ECS boundary node $r$, to have either the bounce-back condition or the reflection condition approximate the zero-flux to second order, we need either

$$C_t = D \left( \frac{1}{2} C_{xx} + C_{yy} + C_{zz} \right) \quad (4.20)$$
or

\[ C_t = D(C_{xx} + C_{yy} + C_{zz}), \]  

respectively. Equation (4.21) is true in the interior of the ECS, but may not be true on the ECS boundary.

As \( \varepsilon \to 0 \), both the bounce-back and the reflection conditions approximate the zero-flux \( C_x = 0 \) to order \( \varepsilon \). Here, we will use the bounce-back condition for the following two reasons. First, when we use the LBE, we proceed with the three successive steps: particle injection, particle collision, and propagation. The bounce-back condition can be obtained by simply altering the local rotation operation (probabilities), i.e., by deflecting the particle entering in the direction \( \mathbf{c}_k \) into the direction \( \mathbf{c}_{k+3}, k = 1, \ldots, 6 \). To achieve the reflection condition, we have to alter both the local rotation operation and the propagation operation. Then the information needed occurs not only at the node \( \mathbf{r} \), but also at its neighbors. Thus, the geometry of the medium is important. Moreover, the computer code is more difficult to write in this case. These are also the major advantages of the LBE over the finite-difference method. Second, the bounce-back condition conserves the mass with each iteration, whereas the reflection condition does not. If we used the reflection condition at \( \mathbf{r} + \mathbf{c}_1 \), the amount \( C(\mathbf{r} + \mathbf{c}_1, t) - C(\mathbf{r}, t) = O(\varepsilon^2) \) would be added to the mass with each iteration.

From (4.5) or (4.6), it is obvious that with the choices of initial condition, the bounce-back membrane boundary condition, and \( Q_i(\mathbf{r}, t) \), the solution is proportional to \( Q \) with proportionality coefficient dependent on \( \mathbf{r} \) and \( t \).

### 4.4 Tortuosity and volume fraction calculations

The assumptions under which the numerical simulations can be performed in the last section match those used to derive the effective diffusion equation (2.19). Actually, the LBE
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(4.5) simulates the diffusion process within the pore space with the zero-flux membrane boundary condition and the zero boundary condition for the lattice $\mathcal{L}$. The effective diffusion equation (2.19) should describe the volume average $< C >_0$ of the numerically simulated solution. We can use the experimental numerical results to compute the tortuosity and the volume fraction of the porous medium, as done by Nicholson and Phillips [57].

In the LBE, the concentration $C$ is discrete in space and the volume average $< C >$ at a node $r = (x, y, z)$ can be defined as the sum of the $C$s over the neighbor nodes of $r$ divided by the total number of neighbor nodes used for averaging. For example, we can choose $M \times M \times M$ neighbors centered at $r$. Thus, if the set of these cubic neighbor nodes is denoted by $\mathcal{N}$, then the volume average of $C$ can be written symbolically as

$$< C >(r,t) = \frac{1}{M^3} \sum_{q \in \mathcal{N}} C(q,t).$$

Similar to the representative elementary volume $V$, the number $M$ is a characteristic parameter of the porous medium, and it is difficult to choose an appropriate value. To avoid this difficulty, Nicholson and Phillips (see [57], Appendix) showed that the solution to (2.19) given by $< C >_0$ can be approximated by the solution $u$ to the equation

$$\frac{D}{\lambda^2} \nabla^2 u + \frac{q}{\alpha} = u_t$$

in a simple medium. Thus, adding homogeneous initial and homogeneous Dirichlet boundary conditions, the intrinsic average $< C >_0$ of the numerical simulation using the LBE (4.5) is approximated by the solution of the system

$$u_t = \frac{D}{\lambda^2} \nabla^2 u + f,$$

$$u(x, y, z, 0) = 0, \quad 0 \leq x, y, z \leq 1,$$

$$u(x, y, z, t) = 0, \quad (x, y, z) \in \partial\Omega,$$

(4.22)
where \( \partial \Omega \) is the boundary of the unit cube \( \Omega = \{(x, y, z) : 0 \leq x, y, z \leq 1\} \) and

\[
\begin{align*}
f(x, y, z, t) &= \frac{Q}{\alpha} \delta(x - \frac{1}{2}) \delta(y - \frac{1}{2}) \delta(z - \frac{1}{2}) H(T - t).
\end{align*}
\]

Here \( Q \) is the source constant, which is approximately \( 6D \varepsilon Q \) for the three-dimensional lattice and is \( 4DQ \) for two dimensions.

The Dirac delta function \( \delta(x) \) cannot be represented by its corresponding Fourier series expansion, the analytic solution of above system (4.22) is a generalized solution. The generalized solution is not convergent, for example, at \( x = 1/2, y = 1/2 \) and \( z = 1/2 \), and consequently is not suitable for computation of tortuosity and volume fraction, so we seek an asymptotic solution. The delta function \( \delta(x) \) can be approximated by

\[
\varphi_\sigma(x) = \frac{1}{\sqrt{\pi \sigma}} e^{-x^2/\sigma^2}
\]

as \( \sigma \) tends to zero. Thus, the source term \( f(x, y, z, t) \) can be approximated by

\[
f_\sigma(x, y, z, t) = \frac{Q}{\alpha} \varphi_\sigma(x - \frac{1}{2}) \varphi_\sigma(y - \frac{1}{2}) \varphi_\sigma(z - \frac{1}{2}) H(T - t).
\]

The analytical series solution of the above diffusion system (4.22) with the source term \( f_\sigma(x, y, z, t) \) instead of \( f(x, y, z, t) \) for \( 0 \leq t \leq T \) is

\[
\begin{align*}
u(x, y, z, t) &= \frac{8Q\lambda^2}{D\alpha \pi^2} \sum_{l=1}^{\infty} \sum_{m=1}^{\infty} \sum_{n=1}^{\infty} \left\{ \frac{a_l a_m a_n}{(l^2 + m^2 + n^2)} \left( 1 - \exp\left(-\frac{D(l^2 + m^2 + n^2)\pi^2 t}{\lambda^2}\right) \right) \sin(l\pi x) \sin(m\pi y) \sin(n\pi z) \right\}.
\end{align*}
\]

where \( 8Qa_la_ma_n/\alpha \) for \( l, m, n = 1, 2, \ldots \), are Fourier coefficients of the function \( f_\sigma \) and each \( a_n \) is given by

\[
\begin{align*}
a_n &= \int_0^1 \varphi_\sigma(x - \frac{1}{2}) \sin(n\pi x) dx \\
&= 2 \sin\left(\frac{n\pi}{2}\right) \int_0^{\frac{1}{2}} \varphi_\sigma(x) \cos(n\pi x) dx.
\end{align*}
\]
For any $a$ and $n$, we have (see Appendix)
\[
  a_n = \sin\left(\frac{n\pi}{2}\right)e^{-\left(\frac{n\pi\sigma}{2}\right)^2/4} + \frac{2}{n\pi^2/2\sigma^2}\sin\left(\frac{n\pi}{2}\right)e^{-1/(4\sigma^2)}(\sigma \sin\left(\frac{n\pi}{2}\right) + p(n, \sigma))
\]  
(4.26)

where $|p(n, \sigma)| \leq \sigma + \sqrt{\pi}/2$.

Now set
\[
U(x, y, z, t) = \frac{u(x, y, z, t)}{8Q}
\]  
(4.27)

and
\[
\beta = \frac{D\pi^2}{\lambda^2}, \quad \gamma = \alpha\frac{D\pi^2}{\lambda^2} = \alpha\beta.
\]  
(4.28)

Then (4.24) can be written as
\[
\gamma U(x, y, z, t) = \sum_{l=1}^{\infty} \sum_{m=1}^{\infty} \sum_{n=1}^{\infty} \frac{a_l a_m a_n \sin(l\pi x) \sin(m\pi y) \sin(n\pi z)}{l^2 + m^2 + n^2} e^{-\left(\frac{(2l+1)^2 + (2m+1)^2 + (2n+1)^2}{4\beta T_0 + \pi^2 \sigma^2}\right)}
\]  
(4.29)

If $t = T_0$ and $t = T$ are large enough, and since $a_n = 0$ for even integer $n$, then from (4.29) and the first term of (4.26), we have the approximations
\[
\gamma U(x, y, z, T_0) \approx B_0(x, y, z) - \sum_{l=0}^{2} \sum_{m=0}^{2} \sum_{n=0}^{2} \left\{ \frac{(-1)^{l+m+n}}{(2l+1)^2 + (2m+1)^2 + (2n+1)^2} \right\} e^{-\left(\frac{(2l+1)^2 + (2m+1)^2 + (2n+1)^2}{4\beta T_0 + \pi^2 \sigma^2}\right)} \times \sin((2l + 1)\pi x) \sin((2m + 1)\pi y) \sin((2n + 1)\pi z)
\]  
(4.30)

and
\[
\gamma U(x, y, z, T) \approx B_0(x, y, z) - \sum_{l=0}^{2} \sum_{m=0}^{2} \sum_{n=0}^{2} \left\{ \frac{(-1)^{l+m+n}}{(2l+1)^2 + (2m+1)^2 + (2n+1)^2} \right\} e^{-\left(\frac{(2l+1)^2 + (2m+1)^2 + (2n+1)^2}{4\beta T + \pi^2 \sigma^2}\right)} \times \sin((2l + 1)\pi x) \sin((2m + 1)\pi y) \sin((2n + 1)\pi z)
\]  
(4.31)
where
\[ B_0(x, y, z) = \sum_{l=0}^{N} \sum_{m=0}^{N} \sum_{n=0}^{N} \frac{(-1)^{l+m+n} e^{-((2l+1)^2+(2m+1)^2+(2n+1)^2)\pi^2\sigma^2/4}}{(2l+1)^2 + (2m+1)^2 + (2n+1)^2} \times \sin((2l+1)\pi x) \sin((2m+1)\pi y) \sin((2n+1)\pi z). \]

Here \( N \) is to be determined, and it depends on the size of \( \sigma \) and on the difference between the solution (4.29) and its approximation (4.30) that is desired. If we denote the error, i.e., the absolute value of the difference between the solution (4.29) and its approximation (4.30) by \( E(N, T_0) \), then, we have (see Appendix)

\[ E(N, T_0) \leq E_0(N, T_0) + \frac{24(2\sigma + \sqrt{\pi}/2)^3}{\pi^{9/2}\sigma^6} e^{-1/(4\sigma^2)} \]
\[ + 3\sqrt{\pi} + 8\pi \sqrt{(\pi\sigma/2)^2 + \beta T_0} + 16\sqrt{\pi((\pi\sigma/2)^2 + \beta T_0)} e^{-40((\pi\sigma/2)^2 + \beta T_0)^3} \]

where \( E_0(N, T_0) \) is the smaller of
\[ 3\sqrt{\pi}^3 + 4\pi^2\sigma + 4\pi^2\sqrt{\pi}\sigma^2 \frac{e^{-(N^2+3N)^2\pi^2\sigma^2}}{32(N^2 + 3N)\pi^3\sigma^3} \]
and
\[ 3e^{-((2N+2)^2+1)\pi^2\sigma^2/4} \frac{|\sin \pi(x - \frac{1}{2})| \sin \pi(y - \frac{1}{2})| \sin \pi(z - \frac{1}{2})|((2N+2)^2 + 2)}{32(N^2 + 3N)\pi^3\sigma^3}. \]

To have a small error of estimation (4.32), we need all three terms on the right side to be small. The first term is small when either (4.33) or (4.34) is small. When \( \sigma \) is small, the second term is exponentially small. To have the third term small, we need \( T_0 \) to be large enough such that \( e^{-40((\pi\sigma/2)^2 + \beta T_0)} \) is small. This actually means that with the approximation (4.30) to (4.29), only after a long time \( T_0 \) of injection, i.e., only when the injected particles are fully distributed in the medium, values of tortuosity and volume fraction can be accurately computed.

Note the difference between (4.33) and (4.34). For a given small \( \sigma \) and a given \( N \), if \((x, y, z)\) is a node such that, for example, \( |\sin \pi(x - \frac{1}{2})| \sin \pi(y - \frac{1}{2})| \sin \pi(z - \frac{1}{2})| \geq \sigma \), then
(4.34) is smaller than (4.33). As \(|\sin \pi (x - \frac{1}{2}) \sin \pi (y - \frac{1}{2}) \sin \pi (z - \frac{1}{2})|\) becomes larger, the error \(E(N, T_0)\) becomes smaller. All these imply that the error \(E(N, T_0)\) is smaller for the point which is farther away from the planes \(x = 1/2\) or \(y = 1/2\) or \(z = 1/2\). In order to get a uniform error \(E(N, T_0)\) for all points, we need to choose \(N\) larger for points which are close or on the planes than those points which are off the planes.

From the numerical simulations, the concentration \(C\) within the pore space can be obtained at each nodal point. Since the LBE simulates the diffusion process within the pore space with the zero-flux membrane boundary conditions and the zero boundary condition on the edges of the lattice, the solution of system (4.22) can be approximated by \(C\), i.e., \(u \approx C\) [57]. Actually we can test this assumption by performing simulations with a simple medium (to represent agar in the experimental situation). Using Nicholson and Phillips' formula ([57], eq. 20), which is valid only for short times in our medium because of different boundary conditions, we obtain values for the diffusion coefficient.

In our simulations, we choose the value \(D = 1 \times 10^{-5}\) \(cm^2/s\), and determination of \(D\) from the simulations based on the Nicholson and Phillips' formula gives \(1.12926 \times 10^{-5}\) \(cm^2/s\).

With the approximation \(u \approx C\) we can calculate \(U(x,y,z,T_0)\) and \(U(x,y,z,T)\) through (4.27) at the nodes of \(L\). Then we can obtain \(\beta\) and \(\gamma\) at each node \((x,y,z)\) within the ECS by solving (4.30) and (4.31) at the times \(T_0 < T\). We used the Newton-Raphson method to compute \(\beta\) and \(\gamma\). Finally, (4.28) yields \(\lambda\) and \(\alpha\). Thus, the local tortuosity \(\lambda\) and the local volume fraction \(\alpha\) at each node can be computed approximately by the combination of the asymptotic solution of (4.22) and the numerical simulation of the LBE (4.5). The tortuosity and volume fraction of the brain as a porous medium then are obtained by averaging the local tortuosity and volume fraction over all points within the ECS.

For two-dimensional porous media, numerical simulations can be performed, and the
tortuosity and the volume fraction can be computed exactly the same as for the three-
dimensional case except we use two-dimensional versions of (4.22), (4.24), (4.30), (4.31)
with $Q = 4DQ$.

For the simple agar medium, both the tortuosity and volume fraction are 1 [57]. As
another test of our assumption that the experimental numerical solution should match
the solution of (4.22), we performed the computations for simple media of two and three
dimensions. For a two-dimensional simple medium, consisting of a $100 \times 100$ lattice with
the choices of $\sigma = 0.01$, $N = 100$, $Q_i = 3$, $N_{T_0} = T/\tau = 9500$, and $N_T = T/\tau = 10000$, the resulting tortuosity and volume fraction were 0.9999 and 1.0003, respectively. For
a three-dimensional simple medium, consisting of a $50 \times 50 \times 50$ lattice with $\sigma = 0.01$, $N = 100$, $Q_i = 3$, $N_{T_0} = T/\tau = 4500$, and $N_T = T/\tau = 5500$, the resulting tortuosity
and volume fraction were 1.0008 and 1.0005, respectively.

4.5 Two-dimensional porous media and numerical results

The ECS in the brain is usually considered to be connected. However, the two-dimensional
porous medium with a porosity as small as 0.2 could not be randomly generated. Chen
et al. [10] used their technique to generate a porous medium in two dimensions which
had a connected porous space with volume fractions above 0.5, but this volume fraction
still is too large. Here, we will generate porous media with connected ECS and porosity
as small as 0.2 in the following ways.

Since the aim here is to study how the geometrical properties of the medium affects
the tortuosity and the volume fraction, we will perform computations for some regular
shapes. e.g., rectangular cell shapes which are in a periodic arrangement and for irregular
cell shapes and arrangements. A type one medium is one having rectangular cells aligned
in two directions and a type two medium is one having rectangular cells aligned in one
direction and staggered in the other direction.

We construct a type-three medium as follows. For generating the pore space with width of, say, three lattice links, we choose three adjacent nodes on the bottom boundary, i.e., along the $x$-axis, of the lattice $\mathcal{L}$. These three nodes are advanced one step in the $y$-direction and kept adjacent, but they can shift either one node to the left or one node to the right, or not shift at all. This shift or lack of shift is determined using a random number generator which produces a sequence of numbers $\eta_i$, $i = 1, 2, \ldots$, between 0 and 1. If either $0 < \eta_i < 0.4$ or $0.6 < \eta_i \leq 1$, then the shift is to the left or right, respectively, and if $0.4 \leq \eta_i \leq 0.6$, then there is no shift. This process continues until the three nodes exit the lattice either through the sides or through the top. The resulting path becomes the pore space of the medium. This procedure then is used starting on the $y$-axis of the lattice $\mathcal{L}$. If the resulting porosity is smaller than the desired value, then repeat this cycle. Also, we can always make the center of the lattice to be in the pore space.

Fig. 4.3 shows the concentration profiles versus time at different positions for three porous media of different types. The solid lines are the numerical results of the LBE model and the dashed lines are the asymptotic solution of the two dimensional version of system (4.22) with $\sigma = 0.01$. All these figures are obtained for 100x100 lattices, and the computations have been carried out until time step 40000. During each time step, 3 unit particles are injected on each link of the center node (50, 50) until time step 20000. The specific node position for each curve is shown in the figure.

Fig. 4.4 shows the tortuosity versus volume fraction for various porous media. Computations have been done with 100x100 lattices and an injection rate $Q_i = 3$ on each link of the central node, the numbers of the time steps $N_{T_0}$ and $N_T$ were set equal to 9500 and 10000, respectively. Figures 4.4A and 4.4B are for the porous media of type one and two, respectively, where the effect of the widths of the ECS is considered. The data are from two sets of media with ECS widths equal to three and four lattice links.
Table 4.1: The average absolute difference and maximum difference between the porosity and volume fraction for the media used in Fig. 4.4.

<table>
<thead>
<tr>
<th>Media Type</th>
<th>Average Absolute Difference</th>
<th>Maximum Difference</th>
</tr>
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<tbody>
<tr>
<td>Type one</td>
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<td>0.0665</td>
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<tr>
<td>Type two</td>
<td>0.0369</td>
<td>0.0765</td>
</tr>
<tr>
<td>Type three</td>
<td>0.0390</td>
<td>0.0846</td>
</tr>
</tbody>
</table>

Fig. 4.4C shows the results for type three media with ECS width equal to three lattice links. When we generate type three media, we use a random number generator. To start the random number generator, we have to give an initial value. Different initial values may lead to a different sequence of numbers, \( \eta_i, \ i = 1, 2, \ldots \), and consequently a series of different porous media. In Fig. 4.4C, (a), (b), (c), and (d) are the tortuosities versus volume fractions for four different series of media produced by four different initial values.

Fig. 4.5 shows plots of the porosity versus the volume fraction for the corresponding media used in Fig. 4.4. Table 4.1 shows the average absolute difference and maximum difference between the porosity and the volume fraction plotted in Fig. 4.5 for three different types of media used in Fig. 4.4. The average absolute difference and the maximum difference are taken over the different media of the same type, and the average absolute difference is computed from

\[
\text{Average absolute difference} = \frac{1}{N_m} \sum_i |\alpha_i - \rho_i|
\]

where the sum is taken over media \( i \) of the same type, \( N_m \) is the total number of the media used for averaging, and \( \rho_i \) is the porosity of medium \( i \).

Computing the local tortuosity \( \lambda \) and the volume fraction \( \alpha \) for each point of the ECS is time consuming and not necessary. For Figures 4.4-4.5, we computed the local tortuosity and volume fraction only for those nodes which were 10, 20, 30, 35, 40, 45 lattice link distances from the central node.
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Figure 4.3: Concentration-time profiles at different positions for three porous media of different types in two dimensions. The solid lines are the numerical results of our LBE model, the dotted lines are from the effective diffusion equation. The widths of the ECS of the media are 3 lattice links. A. The medium is of type one, having aligned cells with a porosity of 0.1931, tortuosity of 1.5849, and volume fraction of 0.1847. B. The medium is of type two, having staggered cells with porosity of 0.1816, tortuosity of 1.6725, and volume fraction of 0.1785. C. A medium of type three. The medium has a porosity of 0.2228, tortuosity of 2.4027, and volume fraction of 0.2007.
Figure 4.4: Tortuosity $\lambda$ versus volume fraction $\alpha$ for various porous media in two dimensions. A. The media are of type one. B. The media are of type two. In A and B, one set of data is from the media with the width of the connective ECS equal to 3 lattice links, and the other one is from the media with width equal to 4 lattice links. C. The media are of type three.
Figure 4.5: Porosity versus volume fraction for the corresponding media used in Fig. 4.4.
A. The media are of type one. B. The media are of type two. C. The media are of type three.
4.6 Three-dimensional porous media and numerical results

In this section, we discuss the generation of three-dimensional porous media and present the results.

First, there is a set of type one media studied by El-Kareh et al. [18]. Each medium is composed of uniform cubic cell shapes which are arranged in ordered periodic arrays where the widths of the connected ECS channels are uniformly constant (See Fig. 4.6). Type one (a) media have the cells aligned in two directions and elongated in one direction; type one (b) media have the cells aligned, staggered, and elongated in each direction; type one (c) media have the cells aligned in three directions; and type one (d) media have the cells aligned in two directions and staggered in one direction.

Second, we will generate type two porous media in a way similar to that of Chen et al. [10]. Initially, we set the entire medium to be void space, then we randomly distribute various sizes of solid cubes inside. The larger solid cubes are distributed before the smaller ones. Later cubes can overlap those previously distributed. This procedure produces a medium with a porosity close to the desired value.

Type three media are a mixture of type one and type two media. We first set up a medium of type one such that the medium has a porosity bigger or smaller than the porosity we want. Then we randomly put in solid or void cubic shapes such that the medium has the desired porosity.

Fig. 4.7 shows concentration profiles versus time at different positions for some porous media. All of these figures were obtained for 50×50×50 lattices, and computations were carried out until time step 15000. During each time step, 3 unit particles were injected on each link of the central node until time step 7500. The specific node position for each curve is indicated. The dashed lines for the diffusion model are the asymptotic solutions of (4.22) with $\sigma = 0.01$. 
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Figure 4.6: A schematic representation of porous media in three dimensions of type one (a), (b), (c), and (d).

Fig. 4.8 shows plots of tortuosity versus volume fraction for various porous media of different types. All computations in the figure have been done with $50 \times 50 \times 50$ lattices and an injection rate $Q_i = 3$ on each link of the central node. To compute the tortuosity $\lambda$ and volume fraction $\alpha$, the numbers of time steps $N_{T_0} = T_0/\tau$ and $N_T = T/\tau$ were set equal to 4000 and 5500, respectively.

Fig. 4.9 shows plots of the porosity versus the volume fraction for the corresponding media used in Fig. 4.8. Table 4.2 shows the average absolute difference and maximum difference between the porosity and the volume fraction plotted in Fig. 4.9 for the three different types of media used in Fig. 4.8.

Up to this point, all of the calculations were performed with a fixed diffusion coefficient $D = \varepsilon^2/(6\tau) = 1.0 \times 10^{-5}$ (cm$^2$/s). Fig. 4.10 shows the relationship between tortuosity and various diffusion coefficients for three porous media of different type.

For Figures 4.8-4.10, we computed the local tortuosity and volume fraction only for those nodes which were 10, 15, 18, 20, 23, 25 lattice link distances from the central node.
Figure 4.7: Concentration versus time profiles at three different positions for three different types of porous media in three dimensions. **A.** The medium is of type one (c) with porosity 0.217, tortuosity 1.2968, volume fraction 0.2026. The width of the ECS channel is 3 lattice links. **B.** A medium of type two with porosity 0.28, tortuosity 1.9601, volume fraction 0.2784. The porous medium was generated by first putting 10×10×10 cubes, then 8×8×8 cubes, ..., finally 2×2×2 cubes. **C.** A medium of type three with porosity 0.20, tortuosity 1.7348, and is generated by first obtaining a medium of type one (c) with porosity 0.249, then randomly putting in 2×2×2 cubes until the medium has porosity 0.20.
Figure 4.8: Tortuosity $\lambda$ versus volume fraction $\alpha$ for various porous media in three dimensions. **A.** Media of the type one (a), (b), (c), (d). The width of the ECS channels is 3 lattice links. **B.** Media of type two. (a) is for a set of media produced by first putting $10 \times 10 \times 10$ cubes, then $8 \times 8 \times 8$ cubes, $\cdots$, finally $2 \times 2 \times 2$ cubes until the porosity is the desired value; (b) is for media by first putting $8 \times 8 \times 8$ cubes; (c) is for media by first putting $12 \times 12 \times 12$ cubes, then $10 \times 10 \times 10$ cubes, and so on; (d) is the plot of the function $\lambda = \alpha^{-\beta/2}$ with $\beta = 0.9939$. **C.** Media of type three, (a) and (b) are for the media produced by first setting the medium of type one (d) with a porosity 0.339 and 0.217, then putting $2 \times 2 \times 2$ cubes; (c) and (d) are for the media produced by first setting the media of type one (c) with porosity 0.333 and 0.217, respectively.
Figure 4.9: Porosity versus volume fraction for the corresponding porous media used in Fig. 4.8. A. The media of type one. B. The media of type two. C. The media of type three.
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<table>
<thead>
<tr>
<th>Media Type</th>
<th>Average Absolute Difference</th>
<th>Maximum Difference</th>
</tr>
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<tbody>
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<td>0.0952</td>
</tr>
<tr>
<td>Type two</td>
<td>0.0717</td>
<td>0.2450</td>
</tr>
<tr>
<td>Type three</td>
<td>0.0541</td>
<td>0.1677</td>
</tr>
</tbody>
</table>

Table 4.2: The average absolute difference and maximum difference between the porosity and volume fraction shown in Fig. 4.9 over the media of the same type used in Fig. 4.8.

Figure 4.10: Tortuosity versus the diffusion coefficient for three different three-dimensional porous media of different type. The type one medium has a porosity of 0.2166 and the ECS has a width of 3 lattice links. The type two medium has a porosity of 0.30. The type three medium has a porosity of 0.20, which was produced from a type one (c) medium with a porosity of 0.282, and then randomly putting in additional $2 \times 2 \times 2$ cubes.
4.7 Discussion

In our LBE model, the concentration $C$ is linearly proportional to the source $Q$, and since $u \approx C$, the variable $U$ in (4.27) is independent of the injection rate $Q$. Therefore, neither the tortuosity $\lambda$ nor the volume fraction $\alpha$ depends on $Q$.

Both the tortuosity and the volume fraction may depend on the number of time steps $N_{T_0} = T_0/\tau$ and $N_T = T/\tau$ used in the computations. However, our computations show that if both $N_{T_0}$ and $N_T$ are large enough, then they have very little effect on the tortuosity and volume fraction. For example, for a three-dimensional medium either of type one with porosity of 0.30 or of type two with porosity of 0.2166, when $N_T - N_{T_0} = 1000$ or $N_T - N_{T_0} = 500$ where $N_T$ is 5500, 6000, 7000, the corresponding tortuosity differences are less than 0.001. We have computed the tortuosities for three different three-dimensional media of different types with diffusion coefficients ranging from $0.6 \times 10^{-5} \text{ cm}^2/\text{s}$ to $1.2 \times 10^{-5} \text{ cm}^2/\text{s}$ (Fig. 4.10). For the medium of type one (c), the tortuosities computed for the diffusion coefficients ($\times 10^5$) 0.6, 0.8, 1.0, 1.2 are 1.2655, 1.2654, 1.2581, 1.2682, respectively, and their biggest difference is 0.0101. For the medium of type two, the maximum tortuosity difference is 0.0222. For the medium of type three, the tortuosity difference is less than 0.0906. In all of these cases, the diffusion coefficients have a small effect on the tortuosity, so the tortuosity apparently does not depend on the diffusion coefficients in this range. Thus, the tortuosity appears to be a purely geometrical factor.

Contrary to the conclusion of El-Kareh et al. [18], the cell shape and the arrangement do affect the tortuosity, and, hence, the effective diffusion coefficient (effective diffusivity) $D_e = D/\lambda^2$. A particle diffusing through an irregular-shaped medium must zigzag along a pathway longer than that through a medium with regular shapes; irregular shapes should increase the tortuosity. Indeed, this is true by comparing the tortuosities of
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three-dimensional type-one media with those of type two (Fig. 4.8A, B). A medium of type one consisting of regular shapes with porosity around 0.2 has a tortuosity less than 1.4. In contrast, a medium of type two was generated by randomly putting various sizes of cubes in the domain allowing some cubes to overlap others that had previously been distributed, so the cell shapes are irregular and the widths of the ECS channels are not constant. A medium of type two with a porosity around 0.2 has a tortuosity as large as 2.4.

The tortuosity of the brain is about 1.6 as determined from experimental data and porous media theory by Nicholson and his colleagues [57], [58]. The ECS of the brain is connected, but the pore space of three-dimensional media of types two and three may have regions which are isolated from the rest of the pore space. Thus, such types of media are not similar to the brain, and, as expected, the calculated tortuosities using the LBE with these media are much larger (Fig. 4.8). For example, three-dimensional media of type three (a) were produced by first constructing a medium of type one (d) with a porosity of 0.339, then inserting additional solid cubes until the medium had the desired porosity. We can see from Fig. 4.8C that as we put in more solid cubes, more ECS channels are blocked, so the corresponding tortuosities become larger. Constructing a medium in this way with a porosity of 0.20 can result in a tortuosity as large as 10.01.

Even with uniform sizes of cell shapes and a periodic arrangement, the difference of the effects between the staggered arrangement and the aligned arrangement on the tortuosity can be significant. Intuitively, a medium with a staggered arrangement would have a larger tortuosity than that with an aligned arrangement. Thus, three-dimensional type-one (b) media should have the highest tortuosities, (c) should have the lowest tortuosities, and the tortuosities of (a), (d) should be between those of (b) and (c). This ordering is indeed true as shown in Fig. 4.8A.

This also is evident with two-dimensional media (Fig. 4.4). A medium of type one or
two with a volume fraction of 0.20 has a tortuosity less than 1.57, whereas a medium of type three has a tortuosity around 2.0. That the staggered arrangement also will increase the tortuosity is evident by comparing Fig. 4.4A with Fig. 4.4B.

With uniform cell sizes and shapes and a periodic arrangement, the effect of the width of the ECS pathway on the tortuosity is not negligible. The wider the connected ECS pathway, the smaller the corresponding tortuosity. This effect can be seen clearly in Fig. 4.4A and Fig. 4.4B.

The porosity in the brain is the proportion of the tissue that comprises the ECS, whereas here the volume fraction is computed by fitting the experimental numerical data with the effective diffusion equation (2.19), so porosity and volume fraction are not necessarily identical. This is especially true for those media with irregular cell shapes and arrangements. Sometimes the difference between them can be very large.

The three-dimensional media of type one have regular cell shapes in periodic arrangements and have neither large holes, i.e., locally enlarged ECS regions, nor dead regions, i.e., totally isolated regions from the remaining ECS. For this type of media, the average absolute difference between the porosity and the volume fraction is small, 0.04136 (Table 4.2), and their differences are around this average value (Fig. 4.9A).

The three-dimensional media of type two and three are highly irregular. For these media, it is possible to have a large hole or a dead region. In the region of a large hole, the local volume fraction is larger than the average value (the volume fraction of the medium) and the corresponding local tortuosity is smaller. Since particles cannot get to a node which is isolated from the other parts of the ECS, from the computations, the local tortuosity at that node is infinity, and the local volume fraction is zero. This means that this node is actually accounted as part of the ICS when the local volume fraction is computed. In a sense, the volume fraction could be thought of as the ratio between the volume of the major connected part of the ECS and the total volume of the medium.
If there are too many unconnected extracellular regions, then the volume fraction and porosity will differ greatly. Indeed, this is shown to be true by the computations we have performed (Fig. 4.9 and Table 4.2). The average absolute difference between the porosity and the volume fraction for three-dimensional media of type two is 0.0717 (Table 4.2).

Media consisting of irregular shapes also cause a large fluctuation of the difference between porosity and volume fraction around the average absolute value (Fig. 4.9B, C); one extreme case is a medium of type two with this difference as large as 0.2450. The average absolute difference over the type-three media in Fig. 4.9C is 0.0541. Similar to the tortuosity, as we block more of the ECS channels, the difference between the porosity and the volume fraction, in general, becomes larger. For example, a medium which was generated by first setting the medium to be type one (c) with porosity 0.333, then randomly putting in additional 2x2x2 cubic cells has a porosity 0.2, but has a volume fraction 0.08. The corresponding tortuosity is 2.75.

The two-dimensional media of types one, two, and three have neither holes nor dead-end regions. The computed average absolute differences are even smaller (Table 4.1), and for most of these media, differences between the porosity and volume fraction are around the average value with small fluctuations (Fig. 4.5). The two-dimensional media of type one were generated by having the rectangular cells aligned in two directions, type-two media were produced by having the cells aligned and staggered in each direction, and type-three media were constructed using our algorithm for the random generation of the pore space. The corresponding average absolute differences between the porosity and the volume fraction for these three types of media are 0.0319, 0.0369, 0.0390, respectively (Table 4.1). Even though the differences between these three values are very small, an important result is that as the medium becomes more irregular, the difference between the porosity and the volume fraction becomes larger.

The possible relationship between the tortuosity and the volume fraction, i.e., Archie's
law, in general, is not true. However, for the three-dimensional media of type two, by letting $\beta = 0.9939$, the computed results can be nicely fitted to Archie's law (Fig. 4.8B(d)), although this value of $\beta$ is not in the range $1/2$ to $2/3$ as suggested by Nicholson and Rice [58], [59]. For other type media, the experimental numerical results cannot be fitted by this relationship.

The tortuosity vs volume fraction in two dimensions and three dimensions are shown in Fig. 4.4 and Fig. 4.8, respectively. Our results show that as the volume fraction decreases, the tortuosity increases. However, the rate of change of the tortuosity with respect to the volume fraction is not the same for all types of media. For two-dimensional type three media, the rate of change of tortuosity with respect to the volume fraction is almost a constant, i.e., the relationship between the tortuosity and the volume fraction can almost be fitted to a straight line. However, this relationship is, in general, not true for other types of media.

For two-dimensional type-one and type-two media and three-dimensional type-one media, as the volume fraction decreases from 1.0 to 0.7, the corresponding tortuosity changes dramatically from 1.0 to 1.3. As the volume fraction decreases further to 0.4, the rate of change of tortuosity with respect to the volume fraction becomes relatively smaller. Finally, as the volume decreases from 0.4 to 0.2, the corresponding tortuosity does not change significantly. It seems that the relationship between the tortuosity and volume fraction can be fitted to a function which is concave down for those regular media.

For three-dimensional media of types two and three, as volume fraction decreases from 1.0, the tortuosity gradually increases. As volume fraction changes from 0.4 to 0.2, the tortuosity increases rapidly. It seems that the tortuosity will tend to infinity as the volume fraction tends to zero.

The tortuosity and the volume fraction have strong influences on the time course and amplitude of the extracellular concentration of particles; this is evident from Fig. 4.7 for
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three-dimensional media and Fig. 4.3 for two-dimensional media that have fixed diffusion coefficients. At an ECS node, a large tortuosity implies a small rate of change of concentration (Figures 4.7 and 4.3C), whereas a small tortuosity leads to a rapidly rising or decaying concentration profile (Figures 4.7 and 4.3A). On the other hand, if the rate of change of the concentration is large, the computed tortuosity will be closer to 1.

4.8 Conclusions

In this chapter, we have modeled ion diffusion in the brain-cell microenvironment by mimicking the experiments carried out by Nicholson and his colleagues. Modeling diffusion of ions in the brain can be done realistically by suitable choice of the medium and by appropriate specification of the detailed movements of particles in this medium. We have chosen the medium to be a lattice of nodes and specified particle movement according to the lattice Boltzmann equation, which accurately represents diffusion. The LBE has been applied to other problems in simple media [14],[30]-[43].

Solving the diffusion equation with a singular function $\delta(x)$ as a source using the conventional method requires us to approximate the delta function $\delta(x)$ as we did in Section 4.4 to compute the tortuosity and the volume fraction, but solving such equations using the LBE (4.5) can be easily achieved by a simple suitable choice of the $Q_i$ as we did in Section 4.3. In addition, the LBE (4.5) is good at dealing with arbitrary boundary geometry; it also has the advantage of dealing with singularities such as point sources or sinks in two dimensions, line sources or sinks in three dimensions.

The model built here is suitable for the diffusion of ions such as TMA and TEA, but it cannot be applied to the movement of, for example, potassium and sodium because these ions can cross the membrane. For such ions, the zero-flux membrane boundary condition is no longer valid. Modeling the movement of potassium is developed in Chapter 5.
Chapter 5

An LCA Model for Potassium Movement within Brain and Its Applications

5.1 Introduction

Extracellular potassium \([K^+]_o\) can accumulate temporarily during a direct iontophoretic point \(K^+\) injection [49], [57], during application of drugs or during neuron activity [75], [76], or during pathological conditions such as hypoxia [66] and ischemia [62]. The dispersal of the accumulated extracellular potassium is affected by many factors. The general conclusion [54], [76] is that the movement of potassium is affected by diffusion in the ECS and ICS, by passive and active transport across the membrane, and by spatial buffering mechanism. It is also believed that the clearances of \([K^+]_o\) are compensated by transport across the blood-brain barrier, and by water movement between different compartments.

The aim of this chapter is to build a theoretical model for the dispersal of the increased extracellular potassium \([K^+]_o\) within the brain when the increased \([K^+]_o\) is brought about by an external iontophoretic injection. As applications of the model, we will study the relative importance of the effects of these various mechanisms on the dispersal of the accumulated potassium. The situation we will model is similar to the experiments carried out by Lux and Neher [49] and Heinemann et al. [32], [33], i.e., the situations when the diffusion in the ECS and ICS, and active and passive membrane transport mechanisms are in effect. The transport across the blood-brain barrier and water movements between different compartments will not be considered since their effect on the potassium dispersal is believed to be relatively small [54]. The spatial buffering is an important mechanism
when there is a current flow, but we postpone the study of this mechanism to the following chapter.

The effective diffusion equation (2.19) can accurately describe the migration of several ions and neurotransmitters, such as TMA and TEA, since the absorption of these ions into cells is slow and small, and consequently the effect can be neglected. However, it is not applicable to ions such as potassium, sodium, and calcium. To derive the effective diffusion equation, many assumptions have been made, one of which is that the concentration across the membrane satisfies a zero-flux transport condition (2.11) or a more general linear flux transport condition (2.20). In fact, the assumptions were used to obtain the effective Fick’s law (2.13). For potassium, the simple zero-flux or the linear flux membrane transport condition is not satisfied. The membrane transport condition actually is related to the membrane potential and the membrane conductance as well as the concentration difference across membrane. These factors make it impossible to describe the movement of the potassium by using Fick’s law or a simple linear modified diffusion equation.

Since Equation (2.19) is unable to accurately describe the movement of potassium, we use the lattice cellular automata (LCA) method or corresponding lattice Boltzmann equation method [15], [16] that is good for implementing complex boundary geometry. In previous chapter, mimicking the experiments carried out by Nicholson and his colleagues on the TMA and TEA diffusion in the brain-cell microenvironment, we built an LCA model for the movement of TMA and TEA. The model corresponds to the averaging model of Nicholson and Phillips [57]. In that model, due to our specific choice of the collision rules and the probabilities, the model cannot directly be applied to the movement of potassium. In this chapter, we will extend that model and modify the collision rules such that the corresponding LBE model can describe the movement of potassium.

This chapter is organized as follows. In Section 5.2, we propose a mathematical model
which governs the movement of potassium after the ions are injected into the ECS. In Section 5.3, we present an LCA model and the related lattice Boltzmann equation. In Section 5.4, we describe how we incorporate those mechanisms affecting the movement of potassium into the LCA model, how we choose the collision rules along the membrane wall and the injection amount to match the membrane transport conditions, and how we do the numerical experiments. In Section 5.5, we present the numerical results.

5.2 Mechanisms and model system for $[K^+]_o$ dispersal

The increased $[K^+]_o$ causes potassium to diffuse from the region with a higher concentration to that with a lower concentration. The diffusion process within the ECS can certainly be described by (1.10), i.e.,

$$\frac{\partial C}{\partial t} = D_0 \nabla^2 C + q$$

(5.1)

where $C$ is the concentration of potassium, $D_0$ is the diffusion coefficient of the potassium within the ECS, $q$ is the source or sink term.

With the experiments on brain tissue carried by Lux et al. [49], Heinemann et al. [32], [33], and Gardner-Medwin [22], the ionic source is usually brought about by an iontophoretic injection at some position $r_0 = (x_0, y_0)$ with some time period $T$. Thus, within the ECS,

$$q = Q \delta(r - r_0) H(T - t)$$

(5.2)

where $\delta$ is the Dirac delta function, $H$ is the Heaviside step function, and $Q$ is the injection amount per unit area per unit time.

Since potassium can easily move into the intracellular space, a non-uniform distribution of $K^+$ in the ECS leads to potassium diffusion within the intracellular (cytoplasmic) space. The governing equation for the intracellular diffusion of potassium is the same as
(5.1) except that the diffusion coefficient \( D \), within the cytoplasm (ICS) may be different from the extracellular diffusion coefficient \( D_0 \), i.e.,

\[
\frac{\partial C}{\partial t} = D_i \nabla^2 C. \tag{5.3}
\]

Within the ICS, there is no external source.

As the potassium is accumulated in the ECS, the kinetic or diffusional forces will cause ion migration across the membrane, the rate at which this net migration proceeds will depend of course upon the concentration difference as well as the potential difference across the membrane. The rate of migration across the membrane depends on the conductances or permeabilities of the membrane. Thus, three factors, i.e., membrane potential, concentration difference, and conductance, jointly determine this passive current flow of the potassium across the membrane. The magnitude and direction of the migration of the potassium must reflect the influences of these three factors and may be given (Page 77, [63]), [80] by

\[
I_d = g_K (V - V_K) \tag{5.4}
\]

where \( g_K \) is the conductance of the membrane, \( V \) is the membrane potential given by the Goldman-Hodgkin-Katz formula (1.5), and \( V_K \) is given by the Nernst equation of potassium (1.2)

The membrane potential in (1.5) depends on the concentration of \( Na^+ \) and \( Cl^- \). The effect on \( V \) of the sodium ion fluxes is not expected to be great because of the small relative permeability of \( Na^+ \). The chloride may affect \( V \); however, its contribution to \( V \) compared with potassium is believed much smaller. Thus, we assume that \( V \) is a variable depending only on the ECS and ICS concentrations of potassium at the membrane through

\[
V = \frac{RT}{F} \ln \left( \frac{[K^+]_o + \gamma}{[K^+]_i + \delta} \right) \tag{5.5}
\]
where \( \gamma \) and \( \delta \) are constants. Another reason we use this simplification is that on the dispersal of the increased potassium, the glial cells play a dominate role. The glial cells are mainly permeable to potassium; thus, the concentrations of sodium and chloride can be treated as a constant. This simplification has been used by Tuckwell and Miura in [80] to model spreading depression waves.

In discharging neurons or by injecting \( K^+ \) in the ECS through iontophoresis, active transport is stimulated by raised intracellular \( Na^+ \) concentration \([Na^+]_i\) as well as by a rise in \([K^+]_o\). There are many quantitative descriptions for the active pump current of ion. For example, the pump current flow was given by (1.7). In [73], there were several formulae for the \( K^+ \)-pump coupled with the \( Na \)-current. Most of them assume that the pump depends on the voltage difference across the membrane. Since we use (5.5) to compute the voltage difference across the membrane, the pump is actually related to the potassium concentrations across the membrane. In [80], Tuckwell and Miura assumed that the pump depends only on the diffusion between the extracellular concentration and its resting value. Here we are interested in the potassium dispersal after it is injected in the ECS, so the main function of the active pump is to reduce the accumulated \([K^+]_o\) to its resting level, it is reasonable that we assume that the active transport (pump) for \( K^+ \) depends only on the difference between the concentration of \([K^+]_o\) and its resting value and use the pump term used by Tuckwell and Miura [80]. The pump is given by

\[
I_p = -f_K(1 - \exp(-r_K([K^+]_o - [K^+]_o^*)) + f_K^* \tag{5.6}
\]

where \( f_K, f_K^*, \) and \( r_K \) are positive constants, and \([K^+]_o^*\) is the resting value of extracellular potassium.

The constant \( f_K^* \) in the pump term is necessary because the choice of the passive transport \( I_d \) means there will be some leakage of \( K^+ \) at the resting levels. The \( f_K^* \) will be selected such that the overall effect of passive and active transport, i.e., \( I_d + I_p \), is
Figure 5.1: Left: A schematic representation of a patch of brain as a porous medium. Right: The representation of one model cell. Ions diffuse in the ICS and ECS coupled with active membrane transport ($I_p$) and passive membrane transport ($I_d$).

zero at the resting levels. The negative sign in (5.6) indicates that the pump decreases the extracellular concentration of $K^+$. Thus, across the membrane, we have passive transport $I_d$ due to the concentration difference and electrical gradient and an active transport $I_p$ stimulated by the increased $[K^+]_o$. The total flux of $K^+$ across the membrane is given by $I_d + I_p$. For the ECS ion concentration, the membrane boundary condition is

$$ J \cdot n = \nabla C \cdot n = I_d + I_p $$

(5.7)

where $n$ is the normal vector pointing outward from the cell. The membrane boundary condition for the ICS concentration is also (5.7).

Therefore, in the ECS, the mathematical model governing the movement of the accumulated potassium $[K^+]_o$ is (5.1) with the membrane condition (5.7) (see Fig. 5.1). Inside each cell (ICS), the mathematical model is (5.3) subject to the membrane transport condition (5.7). Since the geometry of the membrane is complicated, solving such a system using a conventional method such as finite difference method would be very difficult. So we seek a LCA model and use its corresponding LBE to solve it.
5.3 Lattice cellular automata model and lattice Boltzmann equation

The model built in Chapter 4, like the averaging diffusion model obtained by Nicholson and Phillips [57], can accurately describe the migration of ions TMA and TEA. However, due to our specific choices of the collision rules and the probabilities, the diffusion coefficient $D$ in the model derived from the LCA depends only on the space unit $\varepsilon$ and the time unit $\tau$, i.e., $D = \varepsilon^2/6\tau$, not on the position. Since the injected potassium can easily cross the membrane, the potassium will actually diffuse both in the ECS and the ICS. Its diffusion coefficients in ECS and ICS may be different due to, for example, the ionic composition difference. Second, that model does not include an advection term which will appear in Chapter 6. To have a position dependent diffusion coefficient and to have the model include the advection term, we will choose different collision rules and allow resting particles to exist. The LCA model we are going to build is similar to the one in Chapter 4 and can be considered as an extension of that model. For completeness, we present the model using a two-dimensional square lattice $\mathcal{L}$.

We assume that all particles have unit masses, move on the lattice $\mathcal{L}$, and update on the lattice. Each node of the lattice is labeled by the discrete vector $r = (x, y)$, and each particle is associated with it a discrete directional length vector of $c_i$, $i = 0, 1, 2, 3, 4$ where $c_0 = \varepsilon(0, 0)$ is a zero vector, $c_i = \varepsilon(\cos((i-1)\pi/2), \sin((i-1)\pi/2))$, $i = 1, 2, 3, 4$. The $c_i$, $i = 1, 2, 3, 4$ are vectors pointing in one of the four possible directions on the lattice and connecting the node to its nearest neighbors. The $\varepsilon$ is the lattice link length. The $i = 1$ corresponds to the direction along the positive $x$ axis and $i$ increases counterclockwise.

Let $\mathcal{S}$ be a set of all vectors $s = (s_0, s_1, s_2, s_3, s_4)$ such that $s_i$ is a nonnegative integer. A configuration of particles at node $r$ at time $t$ can be described by a random vector $n(r, t) = (n_0, n_1, n_2, n_3, n_4)(r, t)$, with values in the state space $\mathcal{S}$. The value $n_i(r, t) = m$ indicates there are $m$ particles at the node $r$ at time $t$ moving in the direction $c_i$; in
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particular, \( n_0(r, t) = m \) indicates there are \( m \) particles resting at the node \( r \) at time \( t \). A configuration of the lattice \( \mathcal{L} \) at time \( t \) is described by a field

\[
\mathbf{n}_\mathcal{L}(t) = \{ \mathbf{n}(r, t) : r \in \mathcal{L} \}. \tag{5.8}
\]

The evolution of the LCA is a sequential change of configurations \( \mathbf{n}_\mathcal{L}(t) \) of the lattice at discrete time steps \( t = 0, \tau, 2\tau, \ldots \). During each configuration change, the model proceeds with three successive steps: particle injection, collision, and propagation.

Injection operator \( I \): During the particle injection step, substances are placed at some node on the lattice. We can define the injection operation as

\[
I_i : \mathbf{n}_i(r, \cdot) \rightarrow \mathbf{n}_i(r, \cdot) + q_i(r, \cdot)
\]

where \( q_i \) represents the amount of particles gained or lost at the node \( r \) at the time \( t \); it can be either a positive or negative integer, and equals the number of particles gained or lost at the node \( r \) at time \( t \).

In the brain, on the outside or inside of the membrane, ions can be taken up or ejected by the active and passive membrane transports. This phenomenon can certainly be modeled as the number gained or lost on the membrane. In their experiments, Nicholson and Phillips [58], Gardner-Medwin [22], Lux et al. [49], and Heinemann et al. [33] used a constant current iontophoresis circuit to inject ions from a micropipette into the brain-cell microenvironment. This particle injection step was designed to mimic the micropipette injection experiments on the brain tissue in Chapter 4. In addition, this injection operation also will be used to model the biological situation along the membrane of the brain in this chapter. At the injection position of the lattice, \( q_i \) is usually constant for some time period.

Collision operator \( C \): At each node \( r \), particles collide, then propagate. During this collision step, direction of particles movement changes according to some specific
collision rules. Here we chose a very simple collision rule; all particles entering a node including the resting particles will have equal probability \( p_i(r) \) to move in the direction of \( c_i, i = 0, 1, 2, 3, 4 \), respectively, and these probabilities are subject to the normalization condition:

\[
p_0(r) + p_1(r) + p_2(r) + p_3(r) + p_4(r) = 1. \tag{5.9}
\]

To explicitly construct the collision operator, we let \( \xi_i(r, t) : r \in \mathcal{L}, t = \tau, 2\tau, \cdots \), be independent sequences of identically distributed, Bernoulli-type random variables, i.e., \( \xi_i \) is either 1 or 0, satisfying

\[
\xi_0 + \xi_1 + \xi_2 + \xi_3 + \xi_4 = 1
\]

and \( \xi_i = 1 \) with the probability \( p_i \). Using these variables, we then can write the collision operator \( C \) as

\[
C_i : n_i \rightarrow n_i^C = \xi_i \sum_{j=0}^{4} n_j.
\]

Propagation operator \( S \): In the propagation step, each particle moves from its present node \( r \) in the direction \( c_i \) to its nearest-neighbor node \( r + c_i \). The propagation can be expressed as

\[
S_i : n_i(r, t) \rightarrow n_i(r + c_i, t + \tau).
\]

Thus, each configuration change, \( S \cdot C \cdot I \), of the automata is

\[
n_i(r + c_i, t + \tau) = \xi_i \sum_{j=0}^{4} n_j(r, t) + \xi_i \sum_{j=0}^{4} q_j(r, t). \tag{5.10}
\]

This is the lattice gas microdynamical equation; It is fully discrete in space, time, and concentration. Since \( n_i \) is either a positive integer or zero; the results of the computations can be noisy. To avoid this noise, again, we use its average \( N_i = E(n_i) \) and take the average of (5.10). Since the Bernoulli-type random variables \( \xi_i \) are independent of the
occupation numbers \( n_i \) and the injection rates \( q_i \), we obtain

\[
N_i(r + c_i, t + \tau) = p_i(r) \sum_{j=0}^{4} N_j(r, t) + p_i(r) \sum_{j=0}^{4} Q_j(r, t)
\]  

(5.11)

where \( Q_i \) is the average of the source \( q_i \), i.e., \( Q_i = E(q_i) \). Equation (5.11) is the discrete lattice Boltzmann equation (LBE) associated with our system. The LBE (5.11) is discrete in time and space, continuous in the density variable.

Since the lattice gas microdynamical equation (5.10) deals with the discrete integer number \( n_i \), instead, we use the LBE (5.11) to simulate the model in Section 5.2. Like the microdynamical equation (5.10), the LBE (5.11) also can be split into three steps, i.e., particle injection, collision, and propagation. More specifically, the LBE (5.11) can be implemented with the following three steps: particle injection operation \( I_i : N_i(r, t) \rightarrow N_i(r, t) + Q_i(r, t) \), particle collision operation \( C_i : \sum_{j=0}^{4} N_j(r, t) \rightarrow N_i(r, t) = p_i(r) \sum_{j=0}^{4} N_j(r, t) \), and the particle propagation \( S_i : N_i(r, t) \rightarrow N_i(r + c_i, t + \tau) \).

5.4 Applying the LBE to the \( K^+ \) movement and numerical simulation

In this section, our goal is to incorporate the geometrical factors of the brain into the porous medium and to incorporate all mechanisms that affect the potassium dynamics into the LBE (5.11). To accomplish this, we first need to set up a proper porous medium to represent the brain tissue, and we need to choose the specific probabilities and the injection amount \( Q_i \) such that the LBE (5.11) can simulate the model system proposed in Section 5.2.

5.4.1 Brain as a porous medium

As in Chapter 4, the membrane of each cell is chosen to be along the lattice links connecting nearest membrane nodes such that the membrane forms a closed curve which separates the ICS from the ECS. The node on the membrane is called a membrane
boundary node. An ECS node with at least one link connected to a membrane node is referred to as an ECS boundary node, whereas an ICS node with at least one link connected to a membrane node is an ICS boundary node.

In Chapter 4, we defined the porosity of a porous medium as the number of lattice nodes in the pore space divided by the total number of lattice nodes where half of the membrane boundary nodes were accounted for as being the pore space. This definition corresponds to the porosity defined as the ratio between the total volume of the pore space and the total volume of the medium, which is different from the definition of the volume fraction [57]. Even though volume fraction and porosity may be different and are treated as different parameters in Chapter 4, here we will treat them as identical since the media we are going to use have no "dead end" nor dead region, and consequently, the difference between the volume fraction and porosity is small.

The porosity or volume fraction of the brain can be as small as 0.15 [58], and the ECS is usually considered to be connected. The two-dimensional porous medium with such properties cannot be randomly generated. There have been many ways to construct a porous medium. The media could be constructed by obstructing regions with non-intersecting or intersecting spheres in ordered or random arrangements. However, these media hardly apply to the modeling of brain tissue as a porous medium, since the closest packing of non-intersecting spheres gives a volume fraction of 0.2595 (page 417, [31]), and random packing of spheres gives \( \alpha \) in the range 0.38-0.47, which are much larger than the volume fractions of the brain reported [57], [58]. Smaller volume fractions may be achieved by representing the excluded region by overlapping spheres. However, for small volume fraction, the resulting interstitial geometry is very different from that observed. In fact, sections through cells generally show each cell to be surrounded by a extracellular space [58]. The overlapping sphere model predicts "dead end" and dead regions, features rarely observed in tissue section. Therefore, neither non-overlapping nor overlapping...
spheres provides a good representation of observed brain cell geometries.

According to El-Kareh et al [18], the assumption that cell shapes are approximately polyhedral, rather than spherical, is more consistent with observed arrangements of cells in biological tissue, especially when $\alpha$ is small. If cell shapes are assumed to be convex, then they are necessarily polyhedral in the space-filling limit $\alpha \to 0$. Several experimental studies on the three-dimensional arrangement of cells and the packing of other convex, deformable cells have shown that their typical shapes are polyhedral, with an average of 14 faces. Each face corresponds to a neighboring cell. The 14-sided shape was described by Kelvin [38] in the context of bubble shapes. Examples of plant and animal cells are cited by Matzke [51]. Kittrell et al. [39] noted some “cuboidal” cell shapes in light micrographs of cultured normal epithelial cells, and described all their cultures as containing “cell that are polygonal to angular in shape.”

Here, we will use the medium having the simplest possible polyhedral cell shape, i.e., a rectangle. In fact, we basically will use the three types of two-dimensional porous media generated in Chapter 4. The type one medium is one having rectangular cells aligned in two directions in a periodic arrangement. The type two medium is one having the rectangular cells aligned in one direction and staggered in the other direction in a periodic arrangement. The type three medium is the one generated through a random number generator and having relatively irregular cell shapes and arrangement.

The geometry of the ECS of the brain is very complicated, and those media generated in Chapter 4 are certainly not capable of substituting for the real brain tissue. However, the geometrical effects of the brain tissue on ion diffusion are mainly through two characteristic factors: the tortuosity and the volume fraction of the brain tissue [22], [57]. When we set up a porous medium, we need to incorporate these two factors. Fortunately, based on the computation of the tortuosities and volume fractions for various media in Chapter 4, we can choose several suitable media from those produced such that both the
tortuosity and the volume fraction of the brain are incorporated into the porous media we are going to use.

5.4.2 Collision probabilities and injection amount within the ECS and ICS

Introduce a variable density

\[ C(r, t) = \sum_{j=0}^{4} N_j(r, t); \]

thus, we can rewrite the LBE (5.11) as

\[ N_i(r, t + \tau) = p_i(r - c_i)C(r - c_i, t) + p_i(r - c_i)Q(r - c_i, t) \]

where \( Q(r, t) = \sum_{j=0}^{4} Q_j(r, t) \). Summing over \( i \), we have

\[ C(r, t + \tau) = \sum_{i=0}^{4} p_i(r - c_i)C(r - c_i, t) + \sum_{i=0}^{4} p_i(r - c_i)Q(r - c_i, t). \quad (5.12) \]

Taylor expanding \( p_i(r - c_i)C(r - c_i, t) \), for \( i = 1, 2, 3, 4 \), and \( C(r, t + \tau) \) at node \( r \) at time \( t \) with small \( \varepsilon \) and \( \tau \), we have

\[
C(r, t + \tau) = C(r, t) + \tau \frac{\partial C}{\partial t}(r, t) + O(\tau^2),
\]

\[
p_1(r - c_1)C(r - c_1, t) = \{ p_1C - \varepsilon(p_1C)_x + \frac{1}{2}\varepsilon^2(p_1C)_{xx} - \frac{1}{6}\varepsilon^3(p_1C)_{xxx}\}(r, t) + O(\varepsilon^4),
\]

\[
p_2(r - c_2)C(r - c_2, t) = \{ p_2C - \varepsilon(p_2C)_y + \frac{1}{2}\varepsilon^2(p_2C)_{yy} - \frac{1}{6}\varepsilon^3(p_2C)_{yyy}\}(r, t) + O(\varepsilon^4),
\]

\[
p_3(r - c_3)C(r - c_3, t) = \{ p_3C + \varepsilon(p_3C)_x + \frac{1}{2}\varepsilon^2(p_3C)_{xx} + \frac{1}{6}\varepsilon^3(p_3C)_{xxx}\}(r, t) + O(\varepsilon^4),
\]

\[
p_4(r - c_4)C(r - c_4, t) = \{ p_4C + \varepsilon(p_4C)_y + \frac{1}{2}\varepsilon^2(p_4C)_{yy} + \frac{1}{6}\varepsilon^3(p_4C)_{yyy}\}(r, t) + O(\varepsilon^4).
\]

Thus, from the normalization condition (5.9) for the probabilities, at node \( r \) at time \( t \), (5.12) becomes

\[
\frac{\partial C}{\partial t} + O(\tau^2) = \left[ \frac{\partial((p_3 - p_1)C)}{\partial x} + \frac{\partial((p_4 - p_2)C)}{\partial y} \right] \varepsilon
\]
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\[ + \frac{1}{2} \left[ \frac{\partial^2 ((p_1 + p_3)C)}{\partial x \partial x} + \frac{\partial^2 ((p_2 + p_4)C)}{\partial y \partial y} \right] \varepsilon^2 \]

\[ + \frac{1}{6} \left[ \frac{\partial^3 ((p_3 - p_1)C)}{\partial x \partial x \partial x} + \frac{\partial^3 ((p_4 - p_2)C)}{\partial y \partial y \partial y} \right] \varepsilon^3 \]

\[ + \sum_{i=0}^{4} p_i(r - c_i)Q_i(r - c_i, t) + O(\varepsilon^4). \quad (5.13) \]

If the time unit \( \tau \) has the same order of \( \varepsilon \), more specifically, \( \tau = \varepsilon \), as \( \varepsilon \to 0 \), (5.13) becomes

\[ \frac{\partial C}{\partial t} = \left[ \frac{\partial ((p_3 - p_1)C)}{\partial x} + \frac{\partial ((p_4 - p_2)C)}{\partial y} \right] + f \quad (5.14) \]

where \( f(r, t) = \lim_{\tau \to 0} \frac{1}{\tau} \sum_{i=0}^{4} p_i(r - c_i)Q_i(r - c_i, t) \). Thus, the lattice cellular automata model or LBE, at the macroscopic level, actually describes the wave phenomena. However, in this thesis, we do not explore this phenomena.

Now, we assume that the time unit \( \tau \) has the order of \( \varepsilon^2 \), i.e., \( \tau = k\varepsilon^2 \), and that

\[ p_1(r) = p_3(r) = kD_1(r), \quad p_2(r) = p_4(r) = kD_2(r) \quad (5.15) \]

where \( k \) is a positive constant. As \( \varepsilon \to 0 \), from (5.13), we have

\[ \frac{\partial C}{\partial t}(r, t) = \left( \frac{\partial^2 (D_1C)}{\partial x \partial x} + \frac{\partial^2 (D_2C)}{\partial y \partial y} \right)(r, t) + f(r, t) \quad (5.16) \]

where

\[ f(r, t) = \lim_{\tau \to 0} \frac{1}{\tau} \sum_{i=0}^{4} p_i(r - c_i)Q_i(r - c_i, t). \]

Thus, the microscopic level LBE (5.11) actually describes the diffusion phenomenon (5.16) at the continuous macroscopic level. Within the extracellular and intracellular spaces, the movement of the potassium by diffusion is governed by (5.1), (5.3). The derivation of the macroscopic equation (5.16) from the LBE (5.11) shows that we can use the LBE (5.11) to simulate the movement of potassium within the ECS and ICS.

With the experiments on brain tissue, the constant iontophoretic injection for some time period \( T \) occurs only at \( r_0 \). For most of the nodes within the ECS and ICS, the
particle injection step is absent, i.e., \( Q_i = 0, i = 0, 1, 2, 3, 4 \). The only exceptional node is the node \( r_0 \) where the external iontophoretical source is located. Therefore, we assume that \( Q_i(r, t) = Q^* \) if \( r = r_0 \) and \( t \leq T \); \( Q_i(r, t) = 0 \) otherwise, \( i = 0, 1, 2, 3, 4 \). Here the \( Q^* \) is a constant. Thus, we have

\[
\lim_{\varepsilon \to 0} \frac{5Q^*/(k\varepsilon^2)}{5Q^*/(k\varepsilon^2)} \quad \text{if} \quad r = r_0, \quad t \leq T, \quad 0 \quad \text{otherwise.}
\]

For two dimensions, the function

\[
d(r) = \begin{cases} \
1/\varepsilon^2 & \text{if } r = r_0, \\
0 & \text{otherwise}
\end{cases}
\]
tends to the Dirac delta function \( \delta(r - r_0) \) as \( \varepsilon \to 0 \). Thus, we have

\[
f(r, t) = \frac{5Q^*}{k} \delta(r - r_0) H(T - t).
\] (5.17)

Within the ECS, in order that (5.16) which is derived from the LBE (5.11) has the exact form of (5.1), we need to set the local collision probabilities \( p_i \) and the injection amount \( Q_i \) properly. Here, we assume \( p_1(r) = p_2(r) = p_3(r) = p_4(r) = kD_o \) and \( Q^* = kQ/5 \). These assumptions mean that all of the particles, after collision, will move in the direction \( c_i, i = 1, 2, 3, 4 \) with equal probability \( kD_o \). With these choices, a particle staying at rest at the node has a probability \( p_0 = 1 - 4kD_o \), and the corresponding diffusion equation (5.16) becomes exactly (5.1).

Within the ICS, to have (5.16) exactly the same as (5.3), we set \( p_1(r) = p_2(r) = p_3(r) = p_4(r) = kD_i \) and \( Q_i = 0 \). With these choices, the particle staying at rest at the intracellular node has a probability \( p_0 = 1 - 4kD_i \).

5.4.3 Membrane transport, initial, and boundary conditions

If a node \( r \) is a membrane boundary node, but not a boundary node of the lattice \( L \), then since the membrane wall is closed, two of its four neighbor nodes \( r - c_i, i = \)
Figure 5.2: Left: A schematic representation of a cell A. The dark line is the membrane wall which separates the ECS from the ICS. Right: The enlarged part which is around the node b of cell A.

1, 2, 3, 4 are membrane boundary nodes. For example, nodes a – ci, i = 2, 3 are the membrane boundary neighbors of the membrane boundary node a of cell A (Fig. 5.2). The membrane boundary nodes can be divided into two groups. The first group is those corner membrane boundary nodes through which there is no direct link between the ICS and ECS. The membrane boundary nodes a, c, e of cell A (Fig. 5.2) are such examples. Of the four neighbor nodes of node a, two are membrane boundary nodes, and two are in the ECS. The other group is those membrane boundary nodes through which there are direct links between the ICS and ECS. The membrane boundary nodes b, d of cell A are such examples. Of the four neighbor nodes of b, two are membrane boundary nodes, one (node f) is in the ECS, and one (node g) is in the ICS. For the second group of nodes, those links connecting the ECS and ICS can certainly be thought of as channels of the membrane.

For the first group of nodes, there is no direct link between the ICS and the ECS, so the exchange of potassium between the ICS and the ECS does not occur. When we use the LBE to perform numerical simulations, we simply use the bounce-back membrane condition, i.e., reverse the moving directions of all particles, which corresponds to zero-flux across the membrane (Section 4.4). At this type of node, the particle injection step
is absent, i.e., \( Q_i = 0, i = 0, 1, \ldots, 4 \).

If the node is in the second group, there are direct links between the ICS and the ECS, so there is an exchange of potassium between the ICS and the ECS. On the one hand, through the links—the imaginary membrane channels, some of the potassium coming from the ECS might move into the ICS, and some of the potassium coming from the ICS might go to the ECS. Thus, at this membrane node, the extracellular particles may be lost, and the intracellular particles may be gained, and vice versa. On the other hand, since the node is a part of the membrane wall which separates the ICS from the ECS, particles crossing the membrane are certainly not the same as those moving within the ECS and ICS. Not all of those particles coming from the ECS can move into the ICS, so some of those particles may eventually bounce back to the ECS through the extracellular link.

At such a node, there is an ECS boundary node through the extracellular link connecting the membrane node. There is also an ICS boundary node through the intracellular link connecting the membrane. The number of particles at the ECS boundary node is the extracellular concentration, and the number at the ICS boundary node is the intracellular concentration. These two quantities are used to determine the direction of particle movement and magnitude through the passive and active transport across the membrane.

At this type of node, for instance, at membrane boundary node \( b \) of cell A, there are \( C(f,t) \) particles at the ECS boundary node \( f \) (see Fig. 5.3). There are also \( C(g,t) \) particles at the ICS boundary node \( g \). Using \( C(f,t) \) as the extracellular concentration and \( C(g,t) \) as the intracellular concentration at the membrane node \( b \), we can compute the flux \( J \) of potassium at node \( b \) by (5.4) - (5.7). Since the flux is related to the two dimensions, and the flux is the amount transferred per unit time per unit length, the net amount of the particles which can cross the membrane per unit time is the unit length
Figure 5.3: A schematic representation of the injection and collision operations at the membrane node \( \mathbf{b} \) of cell A. In the figure, \( N_4(\mathbf{b},t) = p_4(\mathbf{f})C(\mathbf{f},t) \), \( N_2(\mathbf{b},t) = p_2(\mathbf{g})C(\mathbf{g},t) \), \( Q_4(\mathbf{b},t) = -\varepsilon p_4(\mathbf{f})(I_d + I_p) \), \( Q_2(\mathbf{b},t) = \varepsilon p_4(\mathbf{g})(I_d + I_p) \), \( N_i(\mathbf{b},t) = 0 \), \( Q_i(\mathbf{b},t) = 0 \), for \( i = 0, 1, 3 \).

\( \varepsilon \) times \( I_d + I_p \), i.e., \( \varepsilon(I_d + I_p) \). If \( I_d + I_p \) is positive, there are \( \varepsilon(I_d + I_p) \) particles which move from the ICS to the ECS. If \( I_d + I_p \) is negative, there are \( -\varepsilon(I_d + I_p) \) particles which move from the ECS to the ICS.

This particle movement across the membrane node \( \mathbf{b} \) can be considered as a "source" \( \varepsilon(I_d + I_p) \) or "sink" depending on the sign of \( I_d + I_p \) at the outside node \( \mathbf{f} \) of the membrane and a "sink" \( -\varepsilon(I_d + I_p) \) or "source" at the inside node \( \mathbf{g} \) of membrane. When we use the LBE, this process can be implemented by suitable choice of the injection amount \( Q_i \). For example, at the node \( \mathbf{b} \) (see Fig. 5.3), we let \( Q_4(\mathbf{b},t) = -\varepsilon p_4(\mathbf{f})(I_d + I_p) \), \( Q_2(\mathbf{b},t) = \varepsilon p_2(\mathbf{g})(I_d + I_p) \), and \( Q_0(\mathbf{b},t) = Q_1(\mathbf{b},t) = Q_3(\mathbf{b},t) = 0 \).

Before the injection step, there are \( N_4(\mathbf{b},t) = p_4(\mathbf{f})C(\mathbf{f},t) \) particles coming from the node \( \mathbf{f} \) through the ECS link \( \mathbf{fb} \) having the tendency to cross the membrane (see Fig. 5.3). There are also \( N_2(\mathbf{b},t) = p_2(\mathbf{g})C(\mathbf{g},t) \) from the node \( \mathbf{g} \) through its intracellular link \( \mathbf{gb} \) tending to cross the membrane. After the injection, the new extracellular concentration \( N_4(\mathbf{b},t) + Q_4(\mathbf{b},t) \) still points into the ICS and has the tendency to move into the ICS, whereas the new intracellular concentration \( N_2(\mathbf{b},t) + Q_2(\mathbf{b},t) \) points in an opposite direction. In fact, the new extracellular quantity \( N_4(\mathbf{b},t) + Q_4(\mathbf{b},t) \) should go back to the ECS and participates in the evolution within the ECS. Meanwhile, the new intracellular
concentration $N_2(b, t) + Q_2(b, t)$ should go back to the ICS. Thus, we need to change their moving directions. To accomplish such direction changes, we use the collision operation. We can simply choose the bounce-back collision operation to reverse their moving directions.

After the particle injection and the collision operations, particles propagate along their moving directions. The overall effect of these operations on the ECS boundary node $f$, for example, is mathematically equivalent to

$$C(f, t + \tau) = \sum_{i=0, i \neq 2}^{4} p_i(f - c_i)C(f - c_i, t) + p_4(f)C(f, t) - \varepsilon p_4(f)(I_d + I_p). \quad (5.18)$$

Taylor expanding at the node $f$ at the time $t$ and using the probabilities in previous subsection chosen for the ECS, we obtain

$$C_y(f, t) = I_d + I_p - \left\{C_{xx} + \frac{1}{2}C_{yy} - \frac{C_t}{D_0}\right\}(f, t)\varepsilon + O(\varepsilon^2) \quad (5.19)$$

which, as $\varepsilon \to 0$, is the membrane transport condition (5.7) because the normal vector $n$ is in the positive $y$ direction.

Similarly, for the ICS boundary node $g$, our implementation for the LBE is equivalent to

$$C(g, t + \tau) = \sum_{i=0}^{3} p_i(g - c_i)C(g - c_i, t) + p_2(g)C(g, t) + \varepsilon p_2(g)(I_d + I_p). \quad (5.20)$$

Using the probabilities in the previous subsection for the ICS, we have

$$C_y(g, t) = I_d + I_p + \left\{C_{xx} + \frac{1}{2}C_{yy} - \frac{C_t}{D_i}\right\}(g, t)\varepsilon + O(\varepsilon^2) \quad (5.21)$$

which becomes the membrane transport condition (5.7) as $\varepsilon \to 0$.

Thus, at the membrane node, with the choice of the injection amount $Q_i$ and the collision operation, the membrane transport condition (5.7) can be implemented easily using the injection and collision operations.
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The initial condition $N_i(r,0)$ for the simulations is set to be the ECS resting value $[K^+]_o$ and the ICS resting value $[K^+]_i$ in each direction at each node of the lattice for ECS and ICS, respectively. For the membrane boundary node $r$, if the related link of direction $i$ is a membrane wall, then $N_i(r,0)$ will be set to zero, otherwise $N_i(r,0)$ will be either the ECS resting value $[K^+]_o$ or the ICS resting value $[K^+]_i$ depending on whether the related link is in the ECS or in the ICS, respectively. For example, for the node $a$ of Cell A (Fig. 5.2), we have $N_0(a,0) = N_1(a,0) = N_4(a,0) = 0$, $N_2(a,0) = N_3(a,0) = [K^+]_o$. Whereas for node $b$, $N_0(b,0) = N_1(b,0) = N_3(b,0) = 0$, $N_2(b,0) = [K^+]_o$, $N_4(b,0) = [K^+]_i$.

The boundary conditions of the medium (or Lattice $L$) are chosen as following. If the boundary node of the lattice is in the extracellular phase, we simply set the value of $N_i(r,t)$ to be the constant resting background value $[K^+]_o$, which means that the particles which reach the boundary of the lattice within the ECS that are coming from other nodes will be absorbed. If the boundary node is in the ICS, we choose the bounce-back condition; this is equivalent to that zero-flux of ions at the boundary node of lattice in the ICS. With such choices of the lattice boundary condition, the accumulated potassium can move away only through the ECS.

5.5 Results

In this section, we will perform numerical experiments and present the experimental results. Here, we choose the central node of the lattice as the injection position of particles for some time period, i.e., $r_0$ is the center of the lattice $L$. After the potassium ions have been injected on the lattice, the ions move on the lattice.

In the results given and discussed below, except for those parameters explicitly indicated later on, the parameter values and initial values are given in Table 5.1. The
Table 5.1: Parameter values used in numerical simulation.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Dimension</th>
<th>Parameters</th>
<th>Values</th>
<th>Dimension</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \gamma )</td>
<td>9.0</td>
<td>m M/l</td>
<td>( [K^+]_o )</td>
<td>2.0</td>
<td>m M/l</td>
</tr>
<tr>
<td>( \delta )</td>
<td>200.0</td>
<td>m M/l</td>
<td>( [K^+]_i )</td>
<td>140.0</td>
<td>m M/l</td>
</tr>
<tr>
<td>( r_K )</td>
<td>1.0</td>
<td>l/(m M)</td>
<td>( RT/F )</td>
<td>58.0</td>
<td>mV</td>
</tr>
<tr>
<td>( g_K )</td>
<td>0.3670</td>
<td>m M/(s mV)</td>
<td>( D_o )</td>
<td>( 2.5 \times 10^{-5} )</td>
<td>cm²/s</td>
</tr>
<tr>
<td>( f_K )</td>
<td>10.0</td>
<td>m M/s</td>
<td>( D_i )</td>
<td>( 2.5 \times 10^{-5} )</td>
<td>cm²/s</td>
</tr>
</tbody>
</table>

The value of the constant \( RT/F \) is assumed to be the value when the temperature is 37°C. Many of the parameter values such as \( \gamma, \delta, [K^+]_o, [K^+]_i, RT/F \) were used by Tuckwell and Miura in [80], some of them, such as \( g_K \) and diffusion coefficient \( D_o \), come from the literature [54], [63]. The tortuosity and volume fraction of brain tissue are chosen to be around 1.664 and 0.238 respectively. To our knowledge there are no direct measurements of some of these parameters such as \( r_K, f_K \), and the intracellular diffusion coefficient \( D_i \) in brain tissue. When no specific information is known, we choose physiologically reasonable values. The value of the parameter \( f_K^* \) is determined such that the net flux \( J \) across the membrane in (5.7) at the steady state is zero. With our choices of other parameter values, \( f_K^* = -13.436 \) (m M/liter).

Fig. 5.4 shows the concentration-time profiles at different positions for a medium of type two with volume fraction being 0.238 and tortuosity equal to 1.664. This medium will be used throughout this chapter unless we specifically indicate when we are dealing with the geometrical effects on the dispersal of the extracellular potassium. The figure is obtained for a 100×100 lattice, and the computation has been carried out until time step 40000. During each time step, \( Q^* = 0.5 \) unit particles are injected on each link of the central node (50, 50) until time step 20000. The specific node position for each curve is shown in the figure.

The numerical experiments mimicked the experiments on brain tissues carried out by
Lux et al. [49], Heinemann et al. [32]. Unfortunately, we do not have their actual data, so we are unable to plot our numerical results and their experimental results on the same graph. However, comparing Fig. 5.4 with Fig. 2 in [49], we find that these two figures are quite similar qualitatively. The graph also is analogous to the observations made with $K^+$ sensitive micro-electrodes by Gardner-Medwin and Nicholson [22] and show a number of qualitative features present in their experimental records. The initial rate of rise of the $K^+$ concentration is highest near the node where the particle is injected. Further in the tissue, the slower initial rates of the rise are maintained longer. The maximum amplitude of the concentration of the ECS potassium near the central node is larger than that at node further away. Thus, we conclude that the LBE system and the mathematical model in Section 5.2 can describe the movement of potassium after it is injected into the ECS.

With the exact same environment as of Fig. 5.4, the ionic flux crossing the membrane at several membrane nodes versus time are shown in Fig. 5.5. The specific membrane position for each curve is shown in the figure. The upper part of Fig. 5.5 is the active membrane transport flux in Equation (5.6). The lower part of Fig. 5.5 is the passive membrane transport part of (5.4).

At the beginning of the rising phase during the ionic injection and the beginning of the falling phase after the injection has been switched off, the active transport changes more rapidly than the passive transport. The maximum amplitude of the active transport flux is larger than the passive transport flux.

### 5.5.1 The effects of various mechanisms on the potassium dispersal

Fig. 5.6 shows the concentration-time profiles when some of the mechanisms are turned off. The effects of various mechanisms on the potassium dispersal are compared in the figure. ALL: The solid lines are obtained assuming that the dispersal of the accumulated $[K^+]_o$ are affected by ECS diffusion and ICS diffusion with active and passive membrane
Figure 5.4: Concentration-time profiles at different positions for a porous medium of type two. The tortuosity of the medium is 1.664. The volume fraction is 0.238. In the figure, all mechanisms, i.e., ECS diffusion, ICS diffusion, active and passive membrane transport are in effect on the potassium movement.

Figure 5.5: The active transport $I_p$ and passive transport $I_d$ across the membrane vs the time at different membrane nodes. The porous medium and the computation are those used in Figure 5.4. Upper: The active membrane transport flux. Lower: The passive membrane transport flux.
transport. NOA: The long dashed lines are obtained assuming dispersal by ECS and ICS diffusions with passive transport but without the active membrane transport. NOP: The short dashed lines are obtained by dispersal of ECS and ICS diffusions with the active transport but without the passive membrane transport. NAP: The dotted lines are obtained by the dispersal of ECS diffusion without the transport, neither the active nor the passive transport.

Without the membrane transport, the ICS diffusion has no effect on the dispersal of the injected extracellular potassium \([K^+]_0\). Thus, only the ECS diffusion affects the dispersal of potassium after it is injected. In this case, the model system describes actually the movements of ions such as TMA and TEA which do not cross the membrane as in Chapter 4.

From Fig. 5.6, we can see that both the active transport and passive transport affect the dispersal of the potassium after the potassium ions are injected. The active and passive transport affect the maximum amplitude (peak value) of the concentration profile. With both the active and passive transport present, at node (62,50), for example, the maximum amplitude of the concentration is 5.991. Without the passive transport across the membrane, the maximum amplitude of the injected \(K^+\) is about 6.447. When the active transport across the membrane is not in effect, the maximum amplitude reaches 6.738. The maximum amplitude of the injected \(K^+\) can be as high as 7.327 if neither the active nor the passive transport is in effect. On the other hand, the active and passive transport affect the rate of change of the rising phase of the concentration during the injection period and the rate of change of the falling phase of the concentration after the injection has been switched off. Without the passive transport or without the active transport, the rate of change of the concentration is larger than that with the passive or with the active transport, especially, at the beginning of the rising phase and the falling phase. Such an effect clearly can be seen in Fig. 5.6.
Figure 5.6: Concentration-time profiles at several different positions for the type two medium with volume fraction 0.238, tortuosity 1.664. ALL: The solid lines are obtained by assuming dispersal by all mechanisms, i.e., ECS diffusion and ICS diffusion with active and passive membrane transport. NOA: The long dashed lines, dispersal by all mechanisms without active membrane transport. NOP: The short dashed lines, dispersal by all mechanisms without the passive membrane transport. NAP: The dotted lines are obtained without the membrane transport, neither active transport nor passive transport.

Figure 5.7: Half-time value for decline of $[K^+]_0$ at the center of a $3 \times 3$ lattice release zone as a function of the duration of a proceeding period with a steady release amount $Q^* = 1.0$. ALL: decline expected through all mechanisms. NOA: decline with all mechanisms except active transport. NOP: decline with all mechanisms without passive transport. NAP: decline with ECS diffusion only.
Comparing the effect of the active transport with the effect of the passive transport on the potassium dispersal, we find that the active transport has more effect on the dispersal of potassium than the passive transport. First, the active transport decreases the maximum amplitude of injected $[K^+]_o$ more than the passive transport. In Fig. 5.6, the solid lines (ALL) and the short dashed lines (NOP) obtained with active transport have smaller maximum amplitudes than the long dashed lines (NOA) and the dotted lines (NAP) obtained without active transport, respectively. Second, the active transport affects the rate of concentration change more than the passive transport. At the beginning of the rising phase of the concentration, the rate of concentration change with the active transport is smaller than that with the passive transport. This is evident by comparing the solid lines (ALL) with the long dashed lines (NOA), and by comparing the short dashed lines (NOP) with the dotted lines (NAP). This effect is partially due to the fact that the active transport flux grows faster than the passive transport when the injected $K^+$ is accumulating in the ECS. Third, the active transport needs less time than the passive transport to reduce the elevated $[K^+]_o$ to its resting values. From Fig. 5.6, with the active transport (ALL, NOP), the time to reduce the $[K^+]_o$ to its resting values is about $8 \times 4000$ to $9 \times 4000$ steps, but with the passive transport (NOA, NAP), the time to reduce the $[K^+]_o$ to its resting values is more than $10 \times 4000$ steps.

At the beginning and the end of the experiments, the difference between the dotted lines and solid lines are comparatively hardly distinguishable (Fig. 5.6). Only when the concentration relative to the resting value reaches a certain level, does the difference become noticeable. This effect also can be understood from the active and passive transport flux plotted in Fig. 5.5. Both the active flux and passive flux are of the same shape. However, the active flux has larger magnitude than the passive flux when the concentration of the ECS potassium becomes relatively high.

Fig. 5.7 shows the half-time value of the falling phase of $K^+$ versus the duration of
Chapter 5. LBE for Potassium Movement

the potassium injection. The horizontal axis is the duration of the injection of $K^+$. The vertical axis is the time steps needed for the concentration at the central node to reduce to the half value of the injection amount $Q^*/2 + [K^+]_e$. The half-time value includes both the period of the rising phase during the iontophoretical injection and the falling phase after the injection has been switched off. The units in both directions are time steps. For this figure, a quantity of a constant amount $Q^* = 1.0$ has been placed on the lattice at the center of a $3 \times 3$ lattice release zone.

Fig. 5.7 supports the previous conclusion that both the active and passive transports affect the dispersal of potassium, and the active transport plays a more significant role than the passive transport on the dispersal of potassium. For example, for a 500 time steps period injection, the half-time value is 9127 time steps with both the active and passive transport (ALL). The half-time value is about 12686 time steps without the active transport (NOA), while the half-time value is 10456 time steps without the passive transport (NOP). However, with a very brief injection, the difference between the effects of various mechanisms on the dispersal of potassium is relatively small. For instance, for a 2 step injection period, the half-time value is 75 time steps with the active transport, the half-time value is 76 time steps with the passive transport.

As the injection period increases, the half-time value increases. However, the half-time value increases more rapidly when the injection period is short than that when the injection period is long. From Fig. 5.7, it can be seen that when the injection period reaches to a certain level, the change rate of the half-time value with respect to the injection period is approximately constant, i.e., the half-time value is roughly linearly dependent on the injection period when the injection period is long enough.

Fig. 5.7 also indicates that $K^+$ released by brief injection distributes faster than $K^+$ during and after prolonged continuous injection. In other words, the recovery of
the potassium to its resting level is faster after a single or a short stimulation than after a long stimulation. With all mechanisms involved in the potassium dispersal, the half-time value is actually 443 time steps with a 6 step period injection of particles, the half-time value is 11976 time steps with a 1000 time steps period injection.

5.5.2 Geometrical effects on the potassium dispersal

Fig. 5.8 shows the effects of the various geometries of the porous media on the potassium dispersal. The concentration-time profiles for three different porous media at different positions are plotted in Fig. 5.8. The solid lines are obtained from the numerical experiments with a type one medium. The dashed lines are obtained with the type two medium. The dotted lines are obtained with a type three medium. The type one medium has aligned cells with tortuosity 1.480, volume fraction 0.216. The type two medium is the one previously used having all cells aligned in one direction and staggered in another direction. The type three has the tortuosity 1.871, the volume fraction 0.222. The upper curves are the concentration profiles for nodes being 12 lattice links distance away from the central node. The lower curves are for those nodes which are 35 lattice links away from the central node.

As in the case when the injected ions TMA and TEA are dispersed by only ECS diffusion, the geometrical factors affect the dispersal of the potassium. The irregular medium with high tortuosity slows down the movement of potassium even with membrane transport. The potassium disperses faster through a medium with smaller tortuosity than that through a medium with a larger tortuosity. This result can be observed by comparing the curves of type 1, type 2, and type 3. Type 1 with smallest tortuosity has smallest maximum amplitude of the concentration. The type 3 medium with largest tortuosity has the largest peak value.

If the node is near the central node, higher tortuosity leads to a larger rate of change
Figure 5.8: Concentration-time profiles at several different positions for three different types of media. Type one medium has tortuosity 1.480, volume fraction 0.216. The type two medium has tortuosity 1.664, volume fraction 0.238. The type three medium has tortuosity 1.871, volume fraction 0.222. Upper curves are for those nodes which are 12 lattice links away from the central node. The lower curves are for nodes which are 30 lattice links away from the central node.

The upper curves of Fig. 5.8 indeed support this conclusion. The dashed line for the type two medium increases faster than the solid line for the type one medium, and the dotted line for the type three medium grows faster than the dashed line. If the node of the plotted concentration is far from the central node, the higher tortuosity makes it more difficult for the particles to reach that node. In turn, this leads to a larger delay of the rising phase of the concentration at that node. This is obviously shown from the lower curves of Fig. 5.8. The dotted line for the type three medium goes from below the solid line to above the solid line when the particles are being injected.

Fig. 5.9 shows the concentration-time profiles for three different media of different volume fractions. The media are of the same type, i.e., the two-dimensional type two. The curve (a) is the concentration-time profile obtained for a medium of volume fraction
Figure 5.9: Concentration-time profiles for three different media of same type (type two). The curve (a) is for a medium of volume fraction 0.183, the curve (b) is for a medium of the volume fraction 0.273, the curve (c) is for a medium of volume fraction 0.369. Upper curves are for those nodes which are 12 lattice links away from the central node. The lower curves are for nodes which are 30 lattice links away from the central node.

From Fig. 5.9, we see that the larger the volume fraction, the smaller the peak value of the ECS potassium concentration. For example, at the nodes 12 lattice links away from the central node, the curve (a) for a medium with smallest volume fraction 0.183 has the largest peak value 7.78, the curve (b) for a medium of volume fraction 0.273 has a peak value 5.99, and the curve (c) is obtained from the simulation on a medium with largest volume fraction 0.369, and it has the smallest peak value of 4.85. The volume fraction affects the rate of change during the potassium injection. The larger the volume fraction, the smaller the change rate of the ECS concentration with respect to the time during the rising phase when the injection is in progress and during the falling phase after the injection has been switched off.
Fig. 5.10 shows the half-time value versus the duration of the ECS potassium injection for three different media of different volume fractions. The potassium particles are injected at the center of a $3 \times 3$ lattice release zone. The half-time is the time steps needed for the concentration at the central node to reduce to half the value of the injection amount $Q^*$. The curves (a), (b), and (c) are the half-time values vs the duration of the injection for type two media used in Fig. 5.9 with volume fraction 0.183, 0.273 and 0.369, respectively.

The volume fraction affecting the half-time values can be clearly seen from Fig. 5.10. The smaller the volume fraction of the medium, the longer the half-time value needed for the ECS potassium concentration to reduce to half its value through the corresponding medium. For examples, when the duration of the injection is 6 steps, the half-time value through the medium of volume fraction 0.183 is 554, the half-time value through the medium of volume fraction 0.273 is 443, whereas the half-time value through the medium of volume fraction 0.369 is 428. This also means, the recovery of the accumulated ECS potassium to its resting level is faster in media with larger volume fractions than that in media with smaller volume fractions.

5.6 Conclusion

In this chapter, we proposed a mathematical model governing the potassium behavior in the brain after $K^+$ is injected into the ECS. The model consists of diffusion processes within the ECS and within each cell (ICS) coupled with the active and passive membrane transport conditions subject to the complicated membrane geometries. The dispersal of potassium also is affected by the spatial buffering mechanism. The spatial buffering mechanism is very important, especially when there is a current flow in the brain tissue. In the following chapter, we will incorporate the current flow into the model and study
Figure 5.10: Half-time value as a function of the duration of a proceeding period with a steady release amount $Q^* = 1.0$. (a): the time needed for ECS concentration of central node to decrease to the half value expected through a medium with volume fraction 0.183. (b): the time expected through a medium of volume fraction 0.273. (c): the time expected through a medium of volume fraction 0.369.

its effects on the movement of potassium.
Chapter 6

Using the Lattice Boltzmann Equation to Study $K^+$ Movement With a Current Flow in Brain

6.1 Introduction

When a local build-up of extracellular potassium occurs in neural tissue, depolarization of nerve and glial cell may cause currents to flow through the cells, which will assist in the dispersal of potassium. The current flow through tissue also can be brought about by an external applied current or potential difference across neuronal tissue [22], [23], [60]. The current flow affects the migration of potassium. The migration of potassium also is affected by many other mechanisms [54], [76] such as ECS diffusion, ICS diffusion, and active and passive transport. The diffusion of $K^+$ within the ECS and the ICS is contrained by the geometry of the brain through the tortuosity $\lambda$ and the volume fraction $\alpha$. T

In this chapter, we will build a model for the dispersal of the elevated potassium $[K^+]_o$ through brain tissue when there is a current flow. The elevation of the potassium is caused by the iontophoretic $K^+$ injection [49], [55] at one end of the considered tissue. The current flow is due to an externally applied current or voltage difference across the tissue. The current flows through both the ECS and ICS.

In 1983 [22], Gardner-Medwin proposed a theoretical model for the movement of potassium with current flow. In the model, the Nernst-Planck equation with geometrical
factors incorporated (Eqn. 17, page 402, [22], here will be referred as effective Nernst-Planck equation) was used. The effective Nernst-Planck equation is the effective Fick's law if there is no electric effect. Thus, the use of the effective Nernst-Planck equation implies that the zero-flux or the linear flux membrane transport condition is assumed. The effective Fick's law is at the macroscopic level, the ionic concentration and the ionic flux in the effective Fick's law are viewed as continua by averaging over many cells. The theoretical model for the electrical potential was basically cable theory (page 400-401, [22]). The concentration and the flux together with other quantities such as the membrane potential and current in the cable theory are at the cellular level and are related to an individual cell. However, these two different level quantities are treated as identical in that theoretical model.

The volume averaged model (2.19) given by Nicholson and Phillips is at a macroscopic level. It can handle the complicated geometry of the brain-cell microenvironment by incorporating the tortuosity and volume fraction into the model. This reduces the problem within the complicated medium into a problem within the simple medium, but it cannot be applied to deal with the complicated membrane transport condition. The cable theory model proposed by Gardner-Medwin [22] can handle the complicated transport membrane condition, but it is not suitable to deal with the complicated cellular geometry.

In this chapter, we consider the brain consisting of the ECS and the cytoplasm of the cells of the ICS and propose a mathematical model system. The system will include all those mechanisms which affect the dispersal of the extracellular $[K^+]_o$. Since solving such a system subject to the complicated membrane geometry is impossible using a conventional method, we use the LBE in Chapter 5 to solve it. More specifically, we will solve the mathematical system by incorporating all those mechanisms including the current flow into the LBE (5.11) by choosing the suitable collision probabilities and the
injection amount. The numerical experiments will be performed mimicking the experiments on brain tissues such as the rat neocortex and the cerebellum of anaesthetized rats carried out by Gardner-Medwin et al. [22], [23]. As an application of the LBE model, we will study the effect of the external applied current on the dispersal of the accumulated K\textsuperscript{+}.

This chapter is organized as follows. In Section 6.2, we present a model system for the movement of extracellular potassium incorporating with the current flow. In Section 6.3, we present how we choose the probabilities and the injection amounts in the ECS and ICS such that the LBE (5.11) in Chapter 5 simulates the model system proposed in Section 6.2. In Section 6.4, we describe how we achieve the membrane transport conditions. In Section 6.5, we present the numerical results. Finally, we conclude with a discussion of the model developed here.

### 6.2 Model equations for K\textsuperscript{+} movement in brain

The temporarily accumulated \([K^+]_0\) due to iontophoretic injection or neuronal activity leads to the diffusion of the potassium within the ECS. The potassium is electrical charged, its movement within the ECS also is subject to electrical potential gradients. Therefore, the flux \(\mathbf{J}\) of the potassium within the ECS can be described by the Nernst-Planck equation (1.1) [63], i.e.,

\[
\mathbf{J} = -(D\nabla C + Z_K \frac{DF}{RT} C \nabla \psi)
\]

where \(Z_K\) is the valence of \(K^+\), \(C\) is the concentration of potassium, \(D\) is the diffusion coefficient of \(K^+\) within the ECS, and \(\psi\) is the electrical potential field.

We divide the potential field \(\psi\) into two parts, i.e., \(\psi = \phi + \phi_0\). The first part \(\phi_0\) is the electric potential across the tissue externally brought about by the specific applied current. The second part \(\phi\) is the electric potential due to internal changes of ionic
Chapter 6. LBE for K⁺ Movement With Current Flow

charges of substances within the ECS. \( \phi \) is given by the Poisson-Boltzmann equation [63], [70]

\[
\varepsilon \nabla^2 \phi = -q_e \sum_i Z_i C_i e^{-Z_i q_e \phi / RT}
\]

(6.2)

with boundary conditions along the cell membranes. In (6.2), the sum is taken over all ions including the potassium within the ECS, \( C_i \) is the concentration of \( i \)th ion, \( q_e \) is the charge of an electron, and \( \varepsilon \) is a dielectric permittivity. The ionic concentration changes with time, so does the potential \( \phi \).

The ionic source is usually brought about by an iontophoretic injection at some position \( r_0 = (x_0, y_0) \) with some time period \( T \). Here we are mainly interested in the migration of K⁺ during the flux of K⁺ when there is an external current flow. Thus, the injection position will be chosen to be at the boundary of the tissue rather than in the interior of the ECS. The situation is quite similar to the experiment carried out by Gardner-Medwin and Nicholson [23]. Within the ECS, there is no external injection source. Thus, the conservation of the ionic species

\[
\frac{\partial C}{\partial t} = -\nabla \cdot J
\]

(6.3)

gives the governing equation

\[
\frac{\partial C}{\partial t} = D \nabla^2 C + Z_K \frac{DF}{RT} \nabla \cdot (C \nabla (\phi + \phi_0))
\]

(6.4)

for the movement of potassium within the ECS.

With the experiments on brain tissue such as those in [22], [23], [60], the applied external current across the tissue is usually constant. Thus, the potential gradient \( \nabla \phi_0 \) due to the applied current across the tissue is constant with respect to the spatial variable, especially when we assume that the brain as a porous medium consists of rectangular cell shapes arranged in a periodic arrangement (Fig. 6.1). If we denote \( I_o = DF/(RT) \nabla \phi_0 \),
then the above diffusion equation becomes

\[ \frac{\partial C}{\partial t} = D \nabla^2 C + \mathbf{I}_0 \cdot \nabla C + Z_K \frac{DF}{RT} \nabla \cdot (C \nabla \phi). \quad (6.5) \]

The Poisson-Boltzmann equation (6.2) is subject to the geometry of the cells with the membrane transport condition. Solving (6.2) with membrane geometry and the membrane transport condition is impossible. Fortunately, the inclusion of the electric field in (6.1) is mainly for the study of the spatial buffer mechanism. From the results of Orkand and his colleagues [12], [61] and Gardner-Medwin et al. [23], it seems that the glial cells are the principal cells involved in this spatial buffer mechanism. It is well-known that the glial cells are mainly \([K^+]_o\)-selective membrane. Thus, for simplicity, we assume that the movement of potassium is accompanied with the movement of some nonspecific negatively charged ion species to maintain the local electroneutrality and that other ionic movements will be neglected. The equation for the negatively charged ion species also is assumed to be given by (pages 73-74, [50])

\[ \frac{\partial C_-}{\partial t} = D_- \nabla^2 C_- + \mathbf{I}_0 \cdot \nabla C_- + Z_- \frac{D_- F}{RT} \nabla \cdot (C_- \nabla \phi) \quad (6.6) \]

where \(C_-\) is the concentration of the negatively charged ion. \(D_-\) and \(Z_-\) are the diffusion coefficient and the valence of the nonspecific negatively charged ion, respectively.

From the electroneutrality condition \(Z_K C + Z_- C_- = 0\) and (6.6), we have

\[ \frac{\partial C}{\partial t} = D_- \nabla^2 C + \mathbf{I}_0 \cdot \nabla C + Z_- \frac{D_- F}{RT} \nabla \cdot (C \nabla \phi). \quad (6.7) \]

Thus, eliminating \(\nabla \cdot (C \nabla \phi)\) in (6.5) and (6.7) leads to

\[ \frac{\partial C}{\partial t} = D_o^* \nabla^2 C + \mathbf{I}_0 \cdot \nabla C \quad (6.8) \]

where

\[ D_o^* = \frac{DD_-(Z_K - Z_-)}{Z_K D - Z_- D_-}. \quad (6.9) \]
This approach avoids the calculations of the electrical field \( \phi \) due to the internal change of the ionic charges of substances and absorbs the buffering part caused by the ionic changes into the diffusion coefficient. Here we have no knowledge of the nonspecific negatively charged ions and the diffusion coefficient \( D_- \). The negatively charged ions are associated with the potassium concentration, and perhaps, the diffusion coefficient \( D^* \) is a function of \( K^+ \) concentration. Actually, under many circumstances, electrodiffusion is equivalent to nonlinear diffusion with concentration-dependent diffusivities [70]. Using the diffusion coefficient to absorb \( Ca^{2+} \) buffering has been proposed to model the propagation of intercellular calcium waves by Sneyd et al. [72]. When modeling \( Ca^{2+} \), one way to incorporate \( Ca^{2+} \) buffers into a model is to assume that the diffusion coefficient of \( Ca^{2+} \) is given by the sigmoidal curve of Allbritton et al. [1] and omit the buffer equation entirely. This phenomenological approach is the one we have taken here for the part of buffering which is caused by the variation of \( \phi \).

Equation (6.8) gives the description of potassium movement within the ECS. Since potassium can easily move into the cell (ICS), a non-uniform distribution of \( [K^+] \) will lead to an intracellular gradient, thus, potassium will diffuse within each cell. The governing equation for \( K^+ \) inside each cell can be derived similarly by assuming that
inside each cell the potential gradient $\nabla \phi_0$ due to the external applied current or the voltage gradient is constant with respect to the spatial variables. The governing equation for the ICS diffusion of potassium is the same as (6.8), i.e.,

$$\frac{\partial C}{\partial t} = D^*_i \nabla^2 C + I_i \cdot \nabla C$$ \hspace{1cm} (6.10)

except that the diffusion coefficient $D^*_i$ and the constant $I_i$ within each cell (ICS) may be different from those in the ECS.

The local build-up of the $[K^+]_o$ leads to diffusion of the potassium through the channels across the membrane. The diffusional flux across the membrane is given by (5.4). When $[K^+]_o$ increases, the active transport (pump) may be activated [76]. The main function of the pump here is still to reduce the accumulated $[K^+]_o$ to its resting level, we use the pump (5.6) proposed by Tuckwell and Miura in [80]. Thus, across the membrane, the total flux across the membrane is given by $I_d + I_p$, i.e.,

$$\nabla C \cdot n = (I_d + I_p).$$ \hspace{1cm} (6.11)

Therefore, the dispersal of the accumulated $[K^+]_o$ when there is an external applied current or potential difference is governed by (6.8) in the ECS and (6.10) inside each cell of the ICS coupled by the transport condition (6.11) subject to initial condition and boundary condition.

The initial value is set to be resting values $[K^+]_0^r$ in ECS and $[K^+]_r^i$ in ICS. The boundary condition is given as follows. Within the ICS, we use the zero-flux condition. Within the ECS, along the left end of the considered medium $AD$, we use a constant flux $J = J_0$, along the boundaries in the x-axis direction, we use the zero-flux condition, along the right end boundary $BC$, we use the resting constant background condition $[K^+]_0^r$. Since solving such a system using a conventional method would be very difficult, we use the LBE from the previous chapter.
6.3 Using LBE for the $K^+$ dynamics in ECS and ICS

The LBE (5.11) in Chapter 5 is a sequential change of configurations $n_C(t)$ on a square lattice $L$ at discrete time steps $t = 0, \tau, 2\tau, \ldots$. During each configuration change, the model proceeds with three successive steps: particle injection, collision, and propagation. During the particle injection step, substances are placed at some node on the lattice. During the particle collision step, the direction of particles movement changes according to the specific collision rules. In the propagation step, each particle moves from its present node $r$ in the direction $c$, to its nearest-neighbor node $r + c$, where $r = (x, y)$, $c_0 = (0, 0)$, $c_i = \varepsilon(\cos(i - 1)\pi/2, \sin(i - 1)\pi/2)$, $i = 1, 2, 3, 4$.

In the ECS and ICS, the LBE (5.11) is mathematically equivalent to (5.12). Taylor expanding (5.12) for small $\varepsilon$ and time step $\tau$ leads to (5.13). We assume that the time unit $\tau$ has the order of $\varepsilon^2$, i.e., $\tau = k\varepsilon^2$, and that

$$
p_1(r) = a_1(r) - \frac{1}{2} b_1(r) \varepsilon, \quad p_2(r) = a_2(r) - \frac{1}{2} b_2(r) \varepsilon,
$$

$$
p_3(r) = a_1(r) + \frac{1}{2} b_1(r) \varepsilon, \quad p_4(r) = a_2(r) + \frac{1}{2} b_2(r) \varepsilon
$$

(6.12)

where $k$ is a constant and $a_1(r), a_2(r)$ are positive such that $0 \leq p_i(r) \leq 1$ for $i = 0, 1, 2, 3, 4$ and that the normalization condition (5.9) is satisfied. Denote $D_1(r) = a_1(r)/k$, $D_2(r) = a_2(r)/k$, $c_1(r) = b_1(r)/k$, $c_2(r) = b_2(r)/k$, we obtain, as $\varepsilon \to 0$, the following equation

$$
C_i(r, t) = [(c_1 C)_x + (c_2 C)_y + (D_1 C)_xx + (D_2 C)_{yy}] (r, t) + f(r, t)
$$

(6.13)

where

$$
f(r, t) = \lim_{\tau \to 0} \frac{1}{\tau} \sum_{i=0}^{4} p_i(r - c_i) Q(r - c_i, t).
$$

(6.14)

Thus, the microscopic level LBE (5.11) can actually capture the advection-diffusion phenomenon (6.13) at the continuous macroscopic level. Within the ECS and ICS, the
movement of the potassium is advection-diffusion governed by (6.8) and (6.10). The derivation of the macroscopic level equation (6.13) from the LBE (5.11) shows that we can use the LBE (5.11) to simulate the movement of potassium within the ECS and ICS.

In order that (6.13) has the exact forms of (6.8) in the ECS and (6.10) in the ICS, we let \( a_1(r) = a_2(r) = kD_j^* \) and \( (b_1(r), b_2(r)) = kI_j = k((I_j)_1, (I_j)_2) \), i.e.,

\[
\begin{align*}
    p_1(r) &= k\{D_j^* - \frac{1}{2}(I_j)_1\varepsilon\}, \\
    p_2(r) &= k\{D_j^* - \frac{1}{2}(I_j)_2\varepsilon\}, \\
    p_3(r) &= k\{D_j^* + \frac{1}{2}(I_j)_1\varepsilon\}, \\
    p_4(r) &= k\{D_j^* + \frac{1}{2}(I_j)_2\varepsilon\}
\end{align*}
\]

(6.15)

where \( j \) is either \( o \) or \( i \) representing the ECS or ICS, respectively. With such choices of probabilities \( p_i \), a particle staying at rest at a node will have a probability \( p_0 = 1 - 4kD_j^* \).

Within the ECS and ICS, the external iontophoretic injection does not occur. Thus, for all nodes within the ECS and ICS, the particle injection step is absent, i.e., \( Q_i = 0, \ i = 0, 1, \ldots, 4 \). With such a choice of \( Q_i \), the source term (6.14) becomes

\[
f(r, t) = 0.
\]

(6.16)

When we perform numerical simulations, we actually use the LBE (5.11) rather than the lattice gas dynamical equation (5.10). Thus, we may start by assuming that the LBE (5.11) is the model governing the particle movement. In this way, we may further generalize the foregoing results by assuming that the probabilities \( p_i \) depend on both the position \( r \) and the density \( C(r, t) \). With these assumptions, the discrete LBE (5.11) becomes

\[
N_i(r + c_i, t + \tau) = p_i(r, C(r, t)) \sum_{j=0}^{4} N_j(r, t) + p_i(r, C(r)) \sum_{j=0}^{4} Q_j(r, t).
\]

(6.17)

Corresponding to (6.12), we assume that

\[
p_1(r, C(r, t)) = a_1(r, C(r, t)) - \frac{1}{2} b_1(r, C(r, t))\varepsilon,
\]
Chapter 6. LBE for K⁺ Movement With Current Flow

\[ p_2(r, C(r, t)) = a_2(r, C(r, t)) - \frac{1}{2} b_2(r, C(r, t)) \varepsilon, \]
\[ p_3(r, C(r, t)) = a_1(r, C(r, t)) + \frac{1}{2} b_1(r, C(r, t)) \varepsilon, \]
\[ p_4(r, C(r, t)) = a_2(r, C(r, t)) + \frac{1}{2} b_2(r, C(r, t)) \varepsilon. \]

(6.18)

where \( k, a_1(r, C(r, t)), a_2(r, C(r, t)) \) are positive such that \( 0 \leq a_1(r, C(r, t)) + a_2(r, C(r, t)) \leq 1 \) and \( 0 \leq p_i(r, C(r, t)) \leq 1 \) for \( i = 0, 1, 2, 3, 4 \).

Taylor expanding all the terms at node \( r \) at time \( t \) as we did before and assuming that, as \( \varepsilon \to 0 \) and \( \tau \to 0 \), \( a_1(r, C(r, t)) \varepsilon^2/\tau \to D_1(r, C(r, t)) \) and \( a_2(r, C(r, t)) \varepsilon^2/\tau \to D_2(r, C(r, t)) \), \( b_1(r, C(r, t)) \varepsilon^2/\tau \to c_1(r, C(r, t)) \) and \( b_2(r, C(r, t)) \varepsilon^2/\tau \to c_2(r, C(r, t)) \), from (6.17), we obtain, in the limit of \( \varepsilon \to 0 \)

\[ \frac{\partial C}{\partial t}(r, t) = [(c_1 C)_x + (c_2 C)_y + (D_1 C)_{xx} + (D_2 C)_{yy}] (r, t) + f(r, t). \]

(6.19)

Note that \( c_1, c_2, D_1, D_2 \) are functions of concentration \( C \). The partial differential equation (6.19) obtained in this way is nonlinear. The derivation of the nonlinear equation (6.19) suggests that the microscopic dynamical Boltzmann equation (6.17) may be used to solve the nonlinear diffusion phenomenon in a simple or a porous medium. Thus, this generalization of LBE can be used to model the spatial buffering incorporated into the diffusion coefficient.

6.4 Membrane transport condition

The membrane transport condition (6.11) for ECS and ICS can be incorporated at the membrane node in the same way as in Chapter 5. However, the injection amount here will be different from that in Chapter 5 due to the different probabilities here. The membrane boundary nodes are still divided into two groups. The first group are those corner membrane boundary nodes through which there is no direct link between the ICS and ECS. For this group of nodes, the exchange of potassium between ICS and ECS
does not occur. When we do numerical simulation by using LBE, we simply use the
bounce-back membrane condition, i.e., reversing the moving direction of all particles,
which corresponds to zero flux across the membrane. At this type of node, the particle
injection step is absent, i.e., $Q_i = 0$, $i = 0, 1, \ldots, 4$.

The other group are those membrane boundary nodes through which there are direct
links between the ICS and ECS. These links are thought of as membrane channels between
the ICS and ECS. For this group of nodes, the exchange of potassium between the ICS
and ECS occurs. At such a node, for example, at membrane boundary node $b$ of a cell (see
Fig. 5.3), using $C(f, t)$ as the extracellular concentration and $C(g, t)$ as the intracellular
concentration at the membrane node $b$, we can compute the transport $I_d + I_p$ of potassium
at node $b$ by Equations (5.4) to (5.7). Then, we let $Q_4(b, t) = -\varepsilon b_2(f)C(f) - \varepsilon a_2(f)(I_d + I_p)$, $Q_2(b, t) = \varepsilon b_2(g)C(g) + \varepsilon a_2(g)(I_d + I_p)$, and $Q_0(b, t) = Q_1(b, t) = Q_3(b, t) = 0$.

Before the injection step, there are $A_4(b, t) = p_4(f)C(f, t)$ particles coming from the
node $f$ through the ECS link $fb$ having the tendency to cross the membrane (see Fig. 5.3).
There are also $A_2(b, t) = p_2(g)C(g, t)$ from the node $g$ through its intracellular link $gb$
tending to cross the membrane. After the injection, the new extracellular concentration
$N_4(b, t) + Q_4(b, t)$ still points into the ICS and has the tendency to move into the ICS,
whereas the new intracellular concentration $N_2(b, t) + Q_2(b, t)$ points in an opposite
direction. In fact, the new extracellular quantity $N_4(b, t) + Q_4(b, t)$ should go back to the
ECS and participates in the evolution within the ECS. Meanwhile, the new intracellular
concentration $N_2(b, t) + Q_2(b, t)$ should go back to the ICS. Thus, we need to change
their directions of movement. To accomplish such direction changes, we use the collision
operation. We can simply choose the bounce-back collision operation to reverse their
directions of movement.

After the particle injection and the collision operations, particles propagate along their
directions of movement. The overall effect of these operations on the ECS boundary node
\( f \), for example, is mathematically equivalent to

\[
C(f, t + \tau) = \sum_{i=0, i \neq 2}^{4} p_i(f - c_i)C(f - c_i, t) + p_4(f)C(f, t) - \varepsilon b_2(f)C(f, t) - \varepsilon a_2(f)(I_d + I_p).
\] (6.20)

Taylor expanding at the node \( f \) at the time \( t \), we have

\[
C_t + C + O(\tau^2) = \{(p_3 - p_1)C_x + (p_4)C_y\} \varepsilon + \frac{1}{2}\{(p_1 + p_3)C_{xx} + (p_4)C_{yy}\}\varepsilon^2 + p_0C + p_1C + 2p_4C + p_3C - \varepsilon b_2C - \varepsilon a_2(I_d + I_p) + O(\varepsilon^4).
\] (6.21)

Using the probabilities in the previous subsection chosen for the ECS, we obtain

\[
C_y(f, t) = I_d + I_p + O(\varepsilon)
\] (6.22)

which, as \( \varepsilon \to 0 \), is the membrane transport condition (6.11) because the normal vector \( \mathbf{n} \) points outward from the cell.

Similarly, for the ICS boundary node \( g \), our implementation of the LBE is equivalent to

\[
C(g, t + \tau) = \sum_{i=0}^{3} p_i(g - c_i)C(g - c_i, t) + p_2(g)C(g, t) + \varepsilon b_2(g)C(g, t) + \varepsilon a_2(g)(I_d + I_p).
\] (6.23)

Using the probabilities in the previous subsection for the ICS, we have

\[
C_y(g, t) = I_d + I_p + O(\varepsilon)
\] (6.24)

which becomes the membrane transport condition (6.11) as \( \varepsilon \to 0 \).

Thus, at the membrane node, with the choice of the injection amount \( Q_i \) and the bounce-back collision operation, the membrane transport conditions (6.11) can be implemented easily. Since these two operations occur locally, the geometry of the membrane
does not matter. Note that the injection amount in Chapter 5 depends on the concentration through passive transport $I_d$ and active transport $I_p$. However, here the $Q_1$ directly depends on the transports $I_d$ and $I_p$ as well as the concentration. To accomplish such a transport condition, we only need to distinguish the membrane nodes into two groups for implementing the injection operation. We do not need to treat these two groups of the membrane nodes separately for implementing the collision operations, and we use bounce-back collision operation for all membrane nodes.

The initial condition and the boundary condition in Section 6.2 can be achieved easily. As in Chapter 5, the value $N_i(r, 0)$ for the simulations is set to the resting values $[K^+]_e$, $[K^+]_i$ along each direction at each node of the lattice for ECS, ICS, respectively. For the membrane boundary node $r$, if the related link of direction $i$ is a membrane wall, then $N_i(r, 0)$ will be set to zero, otherwise $N_i(r, 0)$ will be the extracellular resting value $[K^+]_e$ or the intracellular resting value $[K^+]_i$ depending on if the related link is in the ECS or ICS.

The boundary conditions of the medium (or lattice $\mathcal{L}$) are chosen as follows. For boundary nodes of the lattice in the $x$-axis direction, no matter which the nodes are in the ICS or ECS, we use the bounce-back conditions. For the right end boundary nodes of the medium, if the nodes are in the ECS, we simply set the value of $N_i(r, t)$ to be the constant resting background value $[K^+]_e$. If the boundary node is in the ICS, we choose the bounce-back condition. For the left end ($x = 0$) boundary nodes of the medium, if the boundary nodes are in the ICS, we use the bounce-back condition. If the node is in the ECS, we will use a constant flux $C_x = Q$. To achieve this boundary condition by using the LBE, we let the injection amount be $Q_1 = -\varepsilon a_1 + \varepsilon Q$. 
6.5 Results

In this section, we will perform several numerical experiments and present the results. Most of the parameter values and initial values are used in Chapter 5 and are given in Table 5.1. The parameter values come from literature [55], [58], [63], and [80]. $I_o$ and $I_i$ are chosen to be $200\mu m/s$. Since we don't have any information about the nonspecific negative charged ion species, for computation simplicity, we will assume that $D_o^*$ and $D_i^*$ are constants rather than propose formulae relating the diffusion coefficients $D_o^*$ and $D_i^*$ to the ECS and ICS concentrations, respectively. These relationships in this chapter are used to model the spatial buffering due to the internal ionic changes and the internal variation of the potential field in the brain. Another simplifying assumption made is that $I_o = I_i$ and $D_o^* = D_i^*$.

The numerical simulations will be performed for a $300 \times 60$ lattice, and the computation will be carried out until time step 60000. During each time step, $Q_1 = 0.3$ unit particles are injected until time step 30000 on the links which are the left end boundary and in the ECS. The medium we are going to use is of type two of the shape shown in Fig. 6.1 with volume fraction 0.238, and this medium will be used throughout this chapter.

Fig. 6.2 shows concentration-time profiles at different positions. The specific node position for each curve is shown in the figure. The horizontal axis is time with the unit in time steps. The vertical axis is the concentration. The numerical experiments mimicked the experiments with the brain tissue carried out by Gardner-Medwin et al. [22], [23] and also can be related to Okada et al. [60]. The numerical experimental results reproduce qualitatively the experimental results obtained by them (Fig. 6.2). The graph in Fig. 6.2 is analogous to the observations made with $K^+$ sensitive micro-electrode by Gardner-Medwin and Nicholson [23] and show a number of features present in the experimental
records. The initial rate of rise of the $K^+$ concentration is largest near the node where the particle is injected. Further from the node of the injection, the slower initial rates of the rise are maintained longer, and more delay in the rise of $K^+$ can be observed in the figure. At the node further from the node of injection, the $K^+$ concentration even continues to rise for a period after the termination of the injection. For examples, at the node $(20, 32)$ which is 20 lattice links from the left end boundary, the concentration of $K^+$ reaches 4 within 6,000 steps, whereas at the node $(40, 32)$, for concentration of $K^+$ to reach 4 requires 14000 time steps.

More interestingly, at nodes far away from the injection node, the $[K^+]_o$ actually decreases for several hundred time steps, and then increases gradually. This phenomenon will be seen more clearly in Fig. 6.3. Fig. 6.3 shows the ionic fluxes against the time across the membrane at several membrane nodes. The specific membrane position for each curve is shown in the figure. The upper part of Fig. 6.3 is the active membrane transport flux given by Eq. (5.6) and the lower part is the passive membrane transport flux given by (5.4).

In Chapter 5, we have studied the effects of various mechanisms on the potassium dispersal, now we would like to study the effect of the current flow on the potassium dispersal.
6.6 The effect of current flow on $K^+$ dispersal

The current flow affects the potassium movement in brain in two different ways. First, the current flow due to the external applied current affects the potassium dispersal. This effect on the $K^+$ dispersal is believed to be uniform within the ECS and ICS, especially when the brain tissue is assumed to consist of rectangular cells. The current flow due to the internal ionic movements and potential variation in the brain caused by the injection of ionic particles affects the $K^+$ dispersal. The effect of the spatial buffering on the potassium movement due to the internal perturbation of the ionic charges is modeled...
into the variable diffusion coefficient. The spatial buffering leads to the fast dispersal of the extracellular accumulated potassium and in turn to the larger diffusion coefficient.

As we know, the larger the external applied current the larger the corresponding parameters $I_o$ and $I_i$. Thus, the effect of the spatial buffering on the potassium movement due to the external applied electrical current is reflected by the effects of the values of $I_o$ and $I_i$. Varying the external current is equivalent to varying the parameter values of $I_o$ and $I_i$. Figure 6.4 shows the comparisons of the concentration-time profiles at several different positions for different values of $I_o$. The values of $I_o$ used are $I_o = 0, 200, 300$, respectively. The concentration-time profiles in Fig. 6.4 shown are those when the application of the current $I_o$ and the ion flux $J$ are still in progress.

From Fig. 6.4, at nodes close to the source edge, for example, at node $(20, 32)$, we see that as the $I_o = I_i$ increases, the maximum amplitude (peak value) of $[K^+]_o$ decreases. Without the applied current, i.e., $I_o = I_i = 0$, the peak value of $[K^+]_o$ are the largest and is actually larger than 10 at time step 30000. With largest external current, i.e., $I_o = 300$, the peak value of $[K^+]_o$ is the smallest and is about 6.2. Also increasing the current leads to reducing the rate of rise of $[K^+]_o$ during the injection period.

However, at nodes far from the source edge, for example, at node $(129, 32)$, the increase of $I_o = I_i$ raises the peak value of the concentration $[K^+]_o$. With the largest $I_o = 300$, the peak values of $[K^+]_o$ is the largest and is close to 2.4 at time step 30000, whereas with the smallest $I_o = 0$, the peak value of $[K^+]_o$ is the smallest and is less than 2.2 at time step 30000.

At the node (e.g., node $(129, 32)$) far from the injection edge, without the current flow, $[K^+]_o$ is always increasing during the injection, and there is no falling phase of $[K^+]_o$ observed during the injection. The falling period exists when the current is introduced. Actually, during the injection, the larger the current is, the larger the magnitude of the falling phase and the falling period. However, at the node (e.g., node $(20,
near the injection edge, the falling phase is hardly observed. The reason for this is that the effect of the diffusion process is relatively slower than that of the current flow. The current flow tends to move away the potassium and reduces the \([K^+]_0\) at a node, whereas the diffusion process sends the elevated potassium at the edge to that node and increases the \([K^+]_0\). At the node near the injection edge, due to the short distance from the edge, the increase of \([K^+]_0\) brought about by the diffusion overcome the decrease of \([K^+]_0\) by the current flow. Therefore, at the node (20, 32), there is no falling phase of the concentration of \(K^+\) observed during the injection. However, due to the long distance, the increase of \([K^+]_0\) by the diffusion is not enough to compensate for the decrease of \([K^+]_0\) by the current flow or the potential difference at a short time of the initiation of the injection.

At the node far from the injection edge, it is very interesting to see that the rate of rise increases after the falling phase. During the falling phase, the external applied current or the voltage difference across the tissue forces the potassium move away within both the ECS and ICS. For example, at the node (129, 32), during the falling phase, \([K^+]_0\) is below the resting level due to the effect of \(I_o\) and \(I_i\). In the meantime, the \(K^+\) is absorbed into cells, especially through the left end of a cell. The larger the \(I_o\) is, the larger the amount of \(K^+\) is absorbed. During the rising phase, the diffusing particles arrive at node (129, 32) and gradually overcome the effect of the \(I_o\), the relatively higher intracellular \(K^+\) concentration due to the larger \(I_o\) makes less \([K^+]_0\) to be pumped into the cell. Thus, during the rising phase, the \([K^+]_0\) increases faster with larger \(I_o\) than with smaller \(I_o\) or without the applied current \(I_o = 0\).

This preliminary simulation suggests that at the node close to the source, the diffusion process overcomes the effect of the current, but at the node far from the source, the larger current leads to the largest maximum value of \([K^+]_0\) even though the larger current initially leads to the larger falling phases of \([K^+]_0\).
Chapter 6. LBE for $K^+$ Movement With Current Flow

Figure 6.4: Concentration-time profiles at (20, 32) (upper) and (129, 32) (lower). In the figure, the comparisons for various currents $I_o$ are made.
Lux and Neher [49] measured $[K^+]_o$ change at short distances from the source (ca. 50-100 $\mu$m) and concluded that the ECS diffusion plays an important role on the dispersal of the $[K^+]_o$, whereas Gardner-Medwin [22] examined the $[K^+]_o$ change at distances relatively far from the source and concluded that the spatial buffering is the most important mechanism affecting potassium movement. The result here explains why the two different conclusions might be drawn depending on the position of measurement of $[K^+]_o$ in the tissue. If we simply consider the concentration profile at a node close to the source, we might say that the diffusion plays an important rule. However, at the nodes far from the source, we might conclude that the applied current is a more important mechanism affecting the potassium movement.
Chapter 7

Conclusions

7.1 General conclusions

To study the movement of ions in the brain when it is considered as a porous medium, there are many methods such as the homogenization method, network techniques, the volume averaging method, the lattice cellular automata method (LCA), and the corresponding lattice Boltzmann equation (LBE) method. In this thesis, several LCA models have been built for ion diffusion within the extracellular space and for the movement of ions, such as potassium, within the brain by mimicking the experimental situations on brain tissues.

In this thesis, we have shown that the LCA or LBE is an effective method to study the diffusion of extracellular ions and to study ion movements in brain. We believe that the study in this thesis is the first application of the LBE to porous media that incorporates particle injection, rotation (collision), and propagation as three distinct steps in implementing the LBE. The inclusion in the LBE of injection of particles into the media mimics the iontophoretic injection of ionized particles in brain tissue. The injection operation also has been used to model the exchange of ions across the membrane.

The LCA or LBE here has many advantages. First, since the transport condition across the membrane can be incorporated into the LBE by the choice of the injection amount and the collision operation, and since the injection and the collision operations occur locally, i.e., their implementations do not need any information at any other node,
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the geometry of the membrane does not matter. Therefore, in an arbitrarily complex pore-space geometry, accurate calculations of microscopic flow are practical, which is one of the most important advantages of the LCA or the LBE. Using the LBE, we have performed numerical simulations not only on porous medium with regular cell shapes in a periodic arrangement, but also on porous media with irregular cell shapes.

Second, the LCA or LBE, on the macroscopic level, describes the movement of TMA or TEA within the ECS or the movement of potassium in the brain after it is injected into the brain-cell microenvironment. The movement of potassium, for example, is governed by the model system consisting of the diffusion equations in the ECS and inside each cell of the ICS coupled by membrane transport subject to the arbitrary membrane cellular geometries. The LBE acts as a numerical scheme for solving such a system, which is difficult to solve using conventional methods such as finite difference schemes.

Third, on the microscopic level, the LBE is basically a simple sequential change of configurations of the lattice at discrete time steps. During each configuration change, the model progresses with particle injection, particle collision, and particle propagation. All these operations can be simply implemented. The injection operation is an addition. The collision operation is to divide the total concentration into different directions according to the probabilities within the ECS and the ICS or to reverse the direction of the particles at the membrane. The propagation is to send the particle to its neighbor nodes. Incorporating various mechanisms into the LBE provides microscopic detail of the movement of ions and how those various mechanisms affect the movement of ions. This microscopic detail is very important for improving our understanding of ion movements. The detail of the movements of the ions also can be animated using the computer.

An important feature of the models in this thesis is that each cell is considered different, and the $K^+$ concentration within each cell is assumed to depend on the spatial variables, i.e., not constant. The numerical solution of the LBE gives the number of
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particles at each node in the ECS and in the ICS. This discrete distribution represents the discontinuous ionic concentration values in the brain. The model is realistically related to the actual situation in the brain.

Furthermore, the modeling carried out in this thesis can be applied to substance movements in any porous medium. The substance can either cross or not cross the interface between the solid space and pore space. For example, the models can be applied to geophysical applications where tracer chemicals are injected into ground water and then undergo diffusion. We also speculate that this modeling may partially replace the need for some types of diffusion experiments in brain tissue.

There are many other advantages of using the LBE. The algorithm for the LBE is parallel, so massive computations on a larger lattice could be performed on a vector machine. The assumptions used to derive the diffusion equation (2.19), for example, can be satisfied rigorously by suitably choosing the membrane boundary conditions.

In Chapter 4, the LBE has been applied to study the TMA or TEA diffusion in the ECS after it has been injected into the ECS. The LBE method developed there first consists of injecting particles for some time period into the central node (taken to be in the ECS) of the lattice. During the process, the particles are moved at each time step according to the rotation and propagation operations. This produces a record of the concentration of particles at each nodal point at each discrete time. The concentrations at two different times are combined with the results from porous media theory, developed by Nicholson and his colleagues, to evaluate the local tortuosity and local volume fraction. Averaging these quantities over the entire pore space of the lattice yields the tortuosity and volume fraction for the entire medium. Using these quantities in the porous media theory then permits us to compare the time evolutions of the local concentration as computed from the LBE model and from porous media theory. We find this comparison to be very good, and the accuracy of the comparisons is similar to that obtained between
experimental data and porous media theory.

The model in Chapter 4 is suitable for the diffusion of ions such as TMA and TEA, but it cannot be applied to the movement of, for example, potassium and sodium because these ions can cross the membrane. For such ions, The zero-flux membrane boundary condition is no longer valid. Modeling the movement of potassium was developed in Chapter 5.

In Chapter 5, we first proposed a mathematical model governing the potassium behavior within the brain after $K^+$ is injected into the ECS. The model consists of diffusion processes within the ECS and within each cell (ICS) coupled with active and passive membrane transport subject to the complicated membrane geometries. Solving such a system using a conventional method is impossible. So we built a lattice gas cellular automata model and use its corresponding LBE to solve the system.

The LCA model or LBE can be considered as an extension of the LCA in Chapter 4, but the LCA model or the LBE in Chapter 5 has some new properties. The LBE can simulate wave phenomenon and diffusion in the porous medium. The diffusion coefficient derived from the LBE can vary with position, and the LBE also can simulate an advection-diffusion process.

The various mechanisms affecting the movement of potassium have been successively incorporated into the model. The active and passive transport across the membrane have been incorporated into the model by suitable choices of the injection and collision operations, and the ECS and the ICS diffusions have been incorporated into the model by using collision and propagation operations. The geometrical effects of the brain tissue on the movement of potassium are characterized by the tortuosity and volume fraction which have been incorporated into the model by the choice of the brain tissue as a porous medium based on our calculations of tortuosities and volume fractions for various media in Chapter 4.
Mimicking the experiments carried out by Lux and Neher [49] and Heinemann et al. [32], [33] on the potassium movement in the brain-cell microenvironment, the numerical simulations have been performed by using the LBE and the numerical results match qualitatively the experimental results on brain tissues. The concentration-time profiles shown also capture the basic qualitative behavior of the experimental results obtained by Gardner-Medwin et al. [23]. As an application of the numerical simulation on the model, we studied the effects of each specific mechanism on the potassium movement by artificially turning on or off the mechanism. We studied the effects of geometrical factors on the potassium movement by varying the geometrical properties of the medium.

The increase in the extracellular potassium concentration can be caused by a direct iontophoretic point $K^+$ injection [49], or as a result of neuronal activity. The main sources of $K^+$ accumulation are stimulated or spontaneously active neurons, unmyelinated fibers, and unmyelinated terminal arborization of myelinated axons [76]. After the neuronal activity, the ICS concentration of potassium may be less than the resting value $[K^+]_i$ since $K^+$ moved out during the neuronal activity. Our numerical simulation has been performed with the initial resting value $[K^+]_i$ in the ICS and the numerical results seem difficult to apply to the movement of potassium accumulated in the ECS due to the neuronal activity. However, the internal potassium concentration is usually much larger than the external concentration, and the ratio of ICS volume to the ECS volume is around 4 [54]. During the activation of nerve cells, even a substantial accumulation of $[K^+]_o$ in such a narrow ECS needs only a small perturbation of the intracellular concentration. It is because of this situation that we assume that after the neuronal activity, the initial value of the ICS is still at the resting value. Thus, the numerical simulation performed in this chapter can be applied to the movement of the accumulated potassium after neuronal activity.
Chapter 7. Conclusions

The dispersal of potassium is affected by many mechanisms such as ECS and ICS diffusions, membrane transport, and the spatial buffering mechanism. The spatial buffering mechanism is very important, especially when there is a current flow in the brain tissue.

In Chapter 6, we first proposed a model system governing the movement of $K^+$ when there is an external applied current. The mathematical model is a first attempt to distinguish the current flow due to the external applied current from the internal current flow due to the internal ionic changes. The model incorporates the external current flow into the parameters $I_o$ and $I_i$, and incorporates the internal current flow due to ionic movement into the diffusion coefficients $D^*_o$ and $D^*_i$. In the ECS and inside each cell of the ICS, the model is an advection-diffusion equation with the diffusion coefficient $D^*_o$ and $D^*_i$. The $D^*_o$ and $D^*_i$ probably depend on the concentration of potassium. The ECS advection-diffusion is coupled with the ICS advection-diffusion through the membrane transport, i.e., the active (pump) transport and the passive transport across the membrane. This coupling, together with the medium which incorporates the geometrical factors, constitutes the model governing the migration of $K^+$ through the brain tissue.

We used the LBE built in Chapter 5 to solve the model system by incorporating various mechanisms affecting the migration of $K^+$. The diffusion phenomena in the ECS and inside each cell of the ICS are modeled by the choices of the leading-order terms of the collision probabilities $p_i$, $i = 0, 1, 2, 3, 4$. The current flows in the ECS and ICS are incorporated into the LBE by the choices of the first-order perturbation of the collision probabilities. The membrane transports are modeled as the "source" or "sink" inside or outside the membrane and are achieved in the LBE by the choices of the injection amount $Q_i$ and by reversing the directions of the particles movement during the collision operation.

The major difference between the LBEs in Chapter 5 and 6 is that the probabilities $p_i$ are assumed to be constants with first-order perturbations. Another main difference
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is that when we achieve the membrane transport condition at the membrane node, the injection amount $Q_i$ is different from the one in Chapter 5 even when the transport condition across the membrane is the same. In Chapter 6, the $Q_i$ depends on the parameters $I_o$ and $I_i$ as well as on the membrane transport $I_p$ and $I_d$.

In Chapter 6, the numerical simulations are performed with constant diffusion coefficients and externally applied constant current. The numerical results obtained are in good qualitative agreement with the experimental results obtained by Gardner-Medwin et al. [22], [23]. As an application of the model, we have studied the effect of the current on potassium movement.

Modeling the spatial buffering together with the diffusion process in the brain as a porous medium has long been a very difficult problem. First, the complicated geometries of the brain tissue are difficult to incorporate into any model. Second, the electrical potential together with the complicated membrane geometries are difficult to model exactly. Third, the diffusion process coupled with the electrical field in a porous medium is difficult to model and actually has never been studied, even though two phase diffusion processes have been studied using the volume averaging method by Whitaker and others [81].

Dividing the electrical potential into two parts, using the parameters $I_o$ and $I_i$ to model the external current, and using the diffusion coefficient to model the internal ionic changes have opened a new way to study the effect of spatial buffering on the potassium dispersal. However, lacking information of the relationship between the diffusion coefficient and the concentration hinders us from performing more sophisticated numerical simulations to study the effect of the spatial buffering. Obtaining a relationship requires lots of experiments on brain tissue. Finding the relationship is one of my future goals. The approach in Chapter 6 is more to provide a way to study the spatial buffering mechanism than study its sophisticated effects.
7.2 Conclusions about tortuosity and volume fraction and biological significance

In Chapter 4, mimicking the experimental situations on brain tissues, numerical simulations were performed, and the numerical results reproduced the experimental results on brain tissue. As an application of the model, the tortuosities and volume fractions for various artificially generated porous media have been computed by comparing the numerical results with the solution of the volume averaged diffusion equation for TMA or TEA. We found the following results.

The diffusion coefficients have little effect on the tortuosity and the tortuosity appears to be a purely geometrical factor. Contrary to the conclusion of El-Kareh et al. [18], the cell shape and the arrangement do affect the tortuosity. Even with uniform cell sizes and shapes and a periodic arrangement, the media with staggered arrangements have larger tortuosities than those with aligned arrangements. Also, the wider the connected ECS pathway, the smaller the corresponding tortuosity.

The porosity and volume fraction are treated differently in Chapter 4. The porosities are not necessarily identical with the volume fractions for media with irregular cell shapes and arrangements. Sometimes the difference between the porosity and volume fraction can be very large for an irregular medium; however, the difference between them is small for a medium of regular cell shape and arrangement.

As the volume fraction increases, the tortuosity decreases. However, the rate of change of the tortuosity with respect to the volume fraction is not the same for all types of media. For two-dimensional type-three media, the rate of change of tortuosity with respect to the volume fraction is almost a constant, i.e., the relationship between the tortuosity and the volume fraction can almost be fitted to a straight line. However, this relationship is not true for other types of media. Archie's law is true for the three-dimensional media.
of type two, but not true, in general, for any other types of media.

For regular media (e.g., two-dimensional type-one and type-two media and three-dimensional type one media), it seems that the relationship between the tortuosity and volume fraction can be fitted to a function which is concave down. For these regular media, as the volume fraction increases, the rate of change of tortuosity with respect to the volume fraction becomes relatively larger. In particular, as the volume increases from 0.2 to 0.4, the corresponding tortuosity does not change significantly. On the contrary, for irregular media (e.g., three-dimensional media of type two and three), as volume fraction increases, the rate of change of tortuosity with respect to the volume fraction becomes relatively smaller. In particular, as the volume increases from 0.2 to 0.4, the corresponding tortuosity decreases significantly.

As we know, volume fraction changes during ischemia [62], hypoxia [66], and postnatal development [46], but tortuosity does not change significantly. However, during postnatal development after X-irradiation at postnatal days 2-5 [77], when the volume fraction changes from 0.2 to 0.48, the tortuosity decreased significantly. Similar results for the tortuosity and the volume fraction for three-dimensional porous media have been obtained here.

Ischemia, hypoxia, and postnatal development do not cause changes of the basic properties of brain tissue such as connectivity and do not create dead ends or holes in the tissue. Brain tissues are regular media of type one, and even though the volume fraction changes from 0.2 to 0.4 during these pathological conditions, the tortuosity does not change significantly. However, X-irradiation results in cell death, extensive neuron loss, blood-brain barrier damage, i.e., X-irradiation leads to dead ends and holes in brain tissue. Such brain tissue is an irregular media of type two or three, and the tortuosity decreases as the volume fraction changes from 0.2 to 0.48. Our results for different values of the volume fraction and porosity suggest that the volume fraction obtained from the
experiments on brain tissue may not be the ratio of the total ECS volume to the total volume of the brain tissue considered.

Corresponding to the volume fraction 0.2, the three-dimensional media of type two and type three have tortuosities of more than 2.20, much larger than the tortuosity of brain tissue reported. The tortuosity for type-one (a), (b), (c) media with the volume fraction 0.2 are below 1.34; the tortuosity for type one (d) is around 1.42, which is smaller than the tortuosity of 1.55 reported by Nicholson et al. [57], [58]. So all of these media are not typical of brain tissue. However, these computations suggest that type one (b) media, i.e., the media staggered, aligned, and elongated in each direction, is more typical of the brain tissue than any other type.

7.3 Significance of geometrical effects on \([K^+]_o\) dispersal

In Chapter 5, as an application of the numerical simulation of the model, we studied the effects of each specific mechanism on potassium movement by artificially turning on or off it. We studied the effects of geometrical factors on the potassium movement by varying the geometrical properties of the medium. We found that both active and passive membrane transport affect the dispersal of potassium after the ions are injected. However, the active transport plays a more important role than the passive transport. With a very brief injection, the difference in the effect between the active and passive transport is not as large as that with a prolonged injection. Potassium released by brief injection distributes faster than \(K^+\) during and after prolonged continuous injection. Geometrical factors of a medium also affect the dispersal of the accumulated extracellular potassium. An irregular medium slows down the movement of potassium and higher tortuosity makes it more difficult for the particles to move. Larger volume fraction makes the accumulated \([K^+]_o\) disperse faster.
Roberts and Feng [68] examined the influence of age on the clearance of potassium from the ECS of rat hippocampal slices, and they found that $K^+$ transport rates and $[K^+]_0$ clearance are affected by age. The $K^+$ clearance from the ECS was significantly slowed in the middle-aged group compared with the younger group in physiological solutions containing 5 mM and 10 mM glucose. Lehmenkühler et al. [46] determined the ECS volume fraction $\alpha$ and tortuosity $\lambda$ for the gray matter of the somatosensory neocortex and subcortical white matter of the rat during postnatal development; they found that the extracellular volume fraction was largest in the newborn rats and diminished with age. Age causes geometrical change. Since our numerical results show that the geometrical properties affect the clearance of the accumulated potassium, we speculate that the age-related clearance of extracellular potassium is perhaps partly due to the age-related changes in the geometry, such as volume fraction.

As shown by Nicholson and his colleagues [62], [66], during some pathological conditions such as hypoxia and ischemia, the geometrical properties change, for example, the volume fraction of brain tissue changes from 0.2 to 0.4. Our results showing that the geometrical properties affect the clearance of the accumulated ECS potassium suggests that during these pathological conditions the clearance may be different from the normal physiological condition. These pathological conditions may affect the time needed for restoring the accumulated ECS potassium to its resting level.

We know that high $[K^+]_0$ might lead to hypoxia, seizure, or spreading depression and that young animals have larger volume fractions than adults [46]. Even though during these pathological conditions, the volume fractions decrease, the volume fractions in young animals still should be larger than those in adults. Our results on the geometrical effects on the $[K^+]_0$ dispersal suggest that the young animals disperse the accumulated $[K^+]_0$ faster and, consequently, might prevent hypoxia, seizure, and spreading depression more efficiently than adults. This is consistent with the conclusion of Lehmenkühler et
le. [46]. However, their reason was not related to the ECS potassium concentration $[K^+]_0$. Lehmenkuhler et al. found that extracellular volume fraction was largest in newborn rats and diminished with age. Since the large extracellular volume fraction of the neonatal brain could significantly dilute ions, metabolites, and neuroactive substances released from cells, relative to release in adults, they concluded that the large volume fraction in young animals may be a factor in preventing anoxia, seizure, and spreading depression.

Different animals may have different geometries and consequently may have different extracellular volume fractions. Even in the same animal, different regions may have different volume fractions. For example, the measurements for the gray matter of the somatosensory neocortex and subcortical white matter of the adult rat by Lehmenkuhler et al. [46] show that the volume fractions of layer II, III, IV, and white matter are 0.19, 0.20, 0.21, and 0.23, respectively. Our results suggests that the clearance of the accumulated extracellular potassium might depend on the specific animal and the specific tissue.

7.4 Significance of the effect of current flow on $[K^+]_0$.

In Chapter 6, some preliminary numerical simulations were performed, and the numerical results show that the ECS $[K^+]_0$ can be depleted at the nodes close to the source or augmented at the nodes far from the source when currents are passed across the tissue. The larger the current, the more $[K^+]_0$ is depleted at the nodes close to the source or augmented at the nodes far from the source.

The simulation suggests that at the node close to the source, the effect of diffusion overcomes the effect of the current, but at the node far from the source, the current increases the maximum value of $[K^+]_0$ even though the current initially decreases $[K^+]_0$. From this, we conclude that the diffusion plays a dominant role for $[K^+]_0$ movement at
the node close to the source, whereas the current plays a relatively more important role at a node far from the source.

Lux and Neher [49] measured $[K^+]_o$ changes at short distances from the source (ca. 50-100 $\mu m$) and concluded that the ECS diffusion plays an important role on the dispersal of the $[K^+]_o$. Gardner-Medwin [22] examined $[K^+]_o$ changes at distances relatively far from the source and concluded that the spatial buffering is the most important mechanism affecting potassium movement. The preliminary simulation result in Chapter 6 explains why the two different conclusions might be drawn depending on the position of measurement of $[K^+]_o$ in the tissue.

7.5 Future Research

Many brain tissues appear to be homogeneous and isotropic, but some regions of brain have structural anisotropy and heterogeneity. Hippocampus is a region in which heterogeneity in $\alpha$ and anisotropy $\lambda$ was reported [66]. Rice et al. [66] studied anisotropic and heterogeneous diffusion and used the experimental data having computed the tortuosity and volume fraction for hippocampus. The retina appears to be heterogeneous in $\alpha$.

In Chapter 4, we studied the diffusion of ions within the ECS and computed tortuosities and volume fractions for many regular and irregular media. However, many media generated in Chapter 4 are structurally anisotropic. For example, three-dimensional type-one (a), (b), and (d) media, two-dimensional type-two and -three media are to some extent structurally anisotropic. The tortuosity values in the direction of each axis in the rectangular cartesian system may be different. A future research project is to study anisotropic and heterogeneous diffusion using the LCA model and to compute the tortuosity and volume fraction for various structurally anisotropic media.

Calcium is one of the most important ions in biological systems. Calcium waves
occur in a variety of cells. Calcium waves can be initiated by both mechanical and chemical stimulation. In response to mechanical stimulation of a single cell, intercellular $\text{Ca}^{2+}$ waves propagate through airway epithelial and glial cell cultures, providing a mechanism for intercellular communication. An intercellular $\text{Ca}^{2+}$ wave differs from the intracellular waves in that the intercellular wave is the propagation of increases in $\text{Ca}^{2+}$ through multiple cells, whereas the intracellular $\text{Ca}^{2+}$ waves are often associated with $\text{Ca}^{2+}$ oscillations and consist of a spatiotemporal increase in intracellular $\text{Ca}^{2+}$ concentration that spreads across an individual cell.

Intercellular waves propagate to the adjacent cell by the diffusion of inositol 1,4,5-trisphosphate ($\text{InsP}_3$) through the gap junction [72]. Release of $\text{Ca}^{2+}$ from intracellular stores is initiated by $\text{InsP}_3$ via the $\text{InsP}_3$ receptor. These mechanisms affecting calcium movement could be incorporated into the LBE model in the same way as those affecting potassium movement. So we would like to study intercellular calcium waves in the brain by using the LBE and the volume-averaging methods.

In the brain, ion movements, such as potassium movement, are not isolated; their movements are always accompanied with other ionic movements, e.g., sodium or calcium movement. In the future, we will extend the LBE models and the volume-averaging models for multi-species and study their dynamics in the brain.

Spreading depression (SD) is a slow chemical wave phenomenon in the cortex of various brain structures and has been studied extensively in various experimental animals. Recently, SD has been implicated in classic migraine and, therefore, warrants more detailed study. SD involves massive movements of sodium, potassium, and calcium ions in the extracellular space (ECS) by diffusion and across cell membranes. Studying such a phenomenon using the LBE or the volume averaging method is one goal of my future research.

The lattice gas cellular automata and the LBE methods, and the volume-averaging
methods can certainly be applied to study particle movements in any porous media. Studying substance movements in other porous media such as ground water flow and oil recovery is another goal of my future research.

All of those computations are intended to be done in both two- and three-dimensions, and we wish to visualize the results. The computations in this thesis have been done on computer workstations. However, the limitations in speed and storage size have prevented more realistic computations. The use of a supercomputer will allow me to carry out computations with large lattice sizes and use algorithms for the lattice gas and LBE methods in parallel form.
Bibliography


Appendix A

Estimation of Error $E(N, T_0)$

In this Appendix, we will estimate the error $E(N, T_0)$, i.e., the difference between the actual solution (4.29) and its approximation (4.30) in Chapter 4. First, we will give a formula for $a_n$. From (4.25) in Section 4.4, we have

$$a_n = 2 \sin \left( \frac{n\pi}{2} \right) \int_0^{\frac{1}{2}} \varphi_\sigma(x) \cos(n\pi x) dx$$

$$= \sin \left( \frac{n\pi}{2} \right) \frac{2}{\sqrt{\pi} \sigma} \left\{ \int_0^{\infty} e^{-x^2/\sigma^2} \cos(n\pi x) dx - \int_{\frac{1}{2}}^{\infty} e^{-x^2/\sigma^2} \cos(n\pi x) dx \right\}$$

$$= \sin \left( \frac{n\pi}{2} \right) e^{-\frac{(n\pi \sigma)^2}{4}} + \sin^2 \left( \frac{n\pi}{2} \right) \frac{2}{n\pi^{3/2} \sigma} e^{-1/(4\sigma^2)}$$

$$- \sin \left( \frac{n\pi}{2} \right) \frac{4}{n\pi^{3/2} \sigma^3} \int_\frac{1}{2}^{\infty} x e^{-x^2/\sigma^2} \sin(n\pi x) dx.$$

Since

$$\left| \int_\frac{1}{2}^{\infty} x e^{-x^2/\sigma^2} \sin(n\pi x) dx \right| \leq e^{-1/(2\sigma^2)} \int_0^{\infty} (x + \frac{1}{2}) e^{-x^2/\sigma^2} dx$$

$$= \frac{\sigma}{2} e^{-1/(4\sigma^2)} (\sigma + \sqrt{\pi} / 2),$$

we obtain

$$a_n = \sin \left( \frac{n\pi}{2} \right) e^{-\frac{(n\pi \sigma)^2}{4}} + \frac{2}{n\pi^{3/2} \sigma^2} \sin \left( \frac{n\pi}{2} \right) e^{-1/(4\sigma^2)} (\sigma \sin \left( \frac{n\pi}{2} \right) + p(n, \sigma)) \quad (A.1)$$

where $|p(n, \sigma)| \leq \sigma + \sqrt{\pi}/2$.

Note that we use $\varphi_\sigma(x)$ to approximate the delta function $\delta(x)$ as $\sigma \to 0$. When $\sigma$ is very small, the second term of (A.1) is much smaller than the first term. If $n$ is fixed such that $n\sigma < 1$, then the leading-order term of $a_n$ is $\sin(n\pi/2) e^{-\frac{(n\pi \sigma)^2}{4}}$. However,
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as $n \to \infty$, since

$$\sin\left(\frac{n\pi}{2}\right) \int_{\frac{1}{2}}^{\infty} x e^{-x^2/\sigma^2} \sin(n\pi x) dx = \sin\left(\frac{n\pi}{2}\right) \frac{1}{n\pi} \int_{\frac{1}{2}}^{\infty} \frac{2x^2}{\sigma^2} e^{-x^2/\sigma^2} \cos(n\pi x) dx$$

and

$$\left| \int_{\frac{1}{2}}^{\infty} \frac{2x^2}{\sigma^2} e^{-x^2/\sigma^2} \cos(n\pi x) dx \right| \leq \int_{\frac{1}{2}}^{\infty} \left(1 + \frac{2x^2}{\sigma^2}\right) e^{-x^2/\sigma^2} dx = \int_{0}^{\infty} \left(1 + \frac{2(x + 1/2)^2}{\sigma^2}\right) e^{-(x+1/2)^2/\sigma^2} dx \leq \frac{(1 + 4\sigma^2 + 2\sigma)\sqrt{\pi}}{2\sigma} e^{-1/(4\sigma^2)},$$

the leading-order term of $a_n$ is $2\sin^2(n\pi/2)e^{-1/(4\sigma^2)}/(n\pi^{3/2}\sigma)$. The formula (A.1) includes both the leading-order terms for large and small $n$, and actually, it is valid for any positive $\sigma$ and $n$.

Now we prove several facts which will be used for the estimation of $E(N, T_0)$.

**Lemma 1** If $I_{l,m,n} = (2l + 1)^2 + (2m + 1)^2 + (2n + 1)^2$, then we have

$$S = \sum_{l=0}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} \frac{1}{I_{l,m,n}(2l + 1)(2m + 1)(2n + 1)} \leq 3 \quad (A.2)$$

and

$$S(N, a) = \sum_{l=N+1}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} \frac{e^{-l_{l,m,n}a^2}}{I_{l,m,n}} \leq \frac{\{(\sqrt{\pi})^3 + 8\pi a + 16\sqrt{\pi} a^2\} e^{-(4N^2+12N)a^2}}{4^4(N^2 + 3N)a^3} \quad (A.3)$$

where $a$ is a positive constant.

**Proof.** Obviously, the functions $1/(I_{x,y,z}(2x + 1)(2y + 1)(2z + 1))$ and $e^{-I_{x,y,z}a^2}/I_{x,y,z}$ are monotonically decreasing with respect to the variables $x, y, z$. In this section, we will repeatedly use these facts.
The sum $S$ in (A.2) can be written as

$$
S = \sum_{l=0}^{\infty} \sum_{m=1}^{\infty} \sum_{n=1}^{\infty} \frac{1}{I_{l,m,n}(2l+1)(2m+1)(2n+1)} + \sum_{l=0}^{\infty} \sum_{n=1}^{\infty} \frac{1}{I_{l,0,n}(2l+1)(2n+1)} \\
+ \sum_{l=0}^{\infty} \sum_{m=1}^{\infty} \frac{1}{I_{l,m,0}(2l+1)(2m+1)} + \sum_{l=0}^{\infty} \frac{1}{I_{l,0,0}(2l+1)} \\
\equiv S_1 + S_2 + S_3 + S_4. \tag{A.4}
$$

We have

$$
S_1 = \sum_{l=0}^{\infty} \sum_{m=1}^{\infty} \sum_{n=1}^{\infty} \frac{1}{I_{l,m,n}(2l+1)(2m+1)(2n+1)} \\
\leq \sum_{l=0}^{\infty} \sum_{m=1}^{\infty} \int_0^{\infty} \frac{1}{I_{l,m,n}(2l+1)(2m+1)(2x+1)} \, dx \\
= \frac{1}{2} \sum_{l=0}^{\infty} \sum_{m=1}^{\infty} \int_1^{\infty} \frac{1}{(2l+1)^2 + (2m+1)^2 + x^2} \, dx \\
= \frac{1}{4} \sum_{l=0}^{\infty} \sum_{m=1}^{\infty} \frac{\ln(1 + (2l+1)^2 + (2m+1)^2)}{(2l+1)^2 + (2m+1)^2 + x^2} \\
\leq \frac{1}{4} \sum_{l=0}^{\infty} \left\{ \frac{\ln(1 + (2l+1)^2)}{(2l+1)} \int_1^{\infty} \frac{1}{(2l+1)^2 + (2x+1)^2} \, dx \right. \\
+ \frac{1}{(2l+1)} \int_0^{\infty} \frac{1}{(2l+1)^2 + (2x+1)^2} \, dx \} \\
= \frac{1}{16} \sum_{l=0}^{\infty} \left\{ \frac{\ln^2(1 + (2l+1)^2)}{(2l+1)^3} + \frac{1}{(2l+1)^2} \left( \pi - 2 \tan^{-1} \left( \frac{1}{2l+1} \right) \right) \right\} \leq 1. \tag{A.5}
$$

In the above derivation, we have used the inequality $\ln(1 + (2l+1)^2 + x^2) \leq \ln(1 + (2l+1)^2 + x)$ if $x > 0$.

It is very easy to prove that

$$
S_2 = S_3 = \sum_{l=0}^{\infty} \sum_{n=1}^{\infty} \frac{1}{I_{l,0,n}(2l+1)(2n+1)} \\
\leq \sum_{l=0}^{\infty} \int_0^{\infty} \frac{1}{(2l+1)^2 + (2x+1)^2} \, dx \\
= \frac{\ln(1 + (2l+1)^2)}{4(1 + (2l+1)^2)(2l+1)} \leq \frac{1}{2l+1}. \tag{A.6}
$$
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\[ S_4 = \frac{1}{3} + \sum_{l=1}^{\infty} \frac{1}{I_{l,0,0}(2l+1)} \leq 1. \tag{A.7} \]

Thus, from inequalities (A.4)-(A.7), we have proved (A.2).

Now we rearrange $S(N, a)$ as

\[
S(N, a) = \sum_{l=N+1}^{\infty} \sum_{m=1}^{\infty} \sum_{n=1}^{\infty} \frac{e^{-l_{m,n}a^2}}{I_{l,m,n}} + \sum_{l=N+1}^{\infty} \sum_{m=1}^{\infty} \frac{e^{-l_{0,n}a^2}}{I_{l,0,n}}
+ \sum_{l=N+1}^{\infty} \sum_{m=1}^{\infty} \frac{e^{-l_{0,0}a^2}}{I_{l,0,0}}
\equiv S_1(N, a) + S_2(N, a) + S_3(N, a) + S_4(N, a). \tag{A.8} \]

we have

\[
S_1(N, a) = \sum_{l=N+1}^{\infty} \sum_{m=1}^{\infty} \sum_{n=1}^{\infty} \frac{e^{-l_{m,n}a^2}}{I_{l,m,n}} \leq \sum_{l=N+1}^{\infty} \sum_{m=1}^{\infty} \sum_{n=1}^{\infty} \frac{e^{-((2l+1)^2+4m^2+4n^2)a^2}}{(2l+1)^2 + 4m^2 + 4n^2}
\leq \sum_{l=N+1}^{\infty} \int_0^{\infty} \int_0^{\infty} \frac{e^{-((2l+1)^2+4x^2+4y^2)a^2}}{(2l+1)^2 + 4x^2 + 4y^2} \, dx \, dy
\leq \sum_{l=N+1}^{\infty} \frac{e^{-(2l+1)^2a^2}}{(2l+1)^2} \int_0^{\infty} \int_0^{\infty} e^{-(4x^2+4y^2)a^2} \, dx \, dy
\leq \frac{\pi}{16a^2} \sum_{l=N+1}^{\infty} \frac{e^{-(2l+1)^2a^2}}{(2l+1)^2} = \frac{\pi}{16a^2} \sum_{l=N+1}^{\infty} \frac{e^{-(2N+2l+1)^2a^2}}{(2N+2l+1)^2}
\leq \frac{\pi e^{-4(N^2+3N)a^2}}{64(N^2+3N)a^2} \sum_{l=1}^{\infty} \frac{e^{-(2l+1)^2a^2}}{4^4(N^2+3N)a^2} \leq \frac{\pi (3/2)e^{-4(N^2+3N)a^2}}{4^4(N^2+3N)a^2}. \tag{A.9} \]

Similarly, we can prove

\[
S_2(N, a) = S_3(N, a) = \sum_{l=N+1}^{\infty} \sum_{m=1}^{\infty} \frac{e^{-l_{m,0}a^2}}{I_{l,m,0}} \leq \sum_{l=1}^{\infty} \sum_{m=1}^{\infty} \frac{e^{-l_{N+m,0}a^2}}{I_{N+l,m,0}} = \sum_{l=1}^{\infty} \sum_{m=1}^{\infty} \frac{e^{-l_{0,m}a^2}}{I_{l,0,m}} \leq \frac{e^{-4(N^2+3N)a^2}}{4(N^2+3N)} \int_0^{\infty} \int_0^{\infty} e^{-(4x^2+4y^2)a^2} \, dx \, dy
\]
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\[ S_4(N, a) = \sum_{i=N+1}^{\infty} \frac{e^{-l_i,0,0a^2}}{I_{l_i,0,0}} \leq \frac{\sqrt{\pi} e^{-4(N^2 + 3N)a^2}}{4^2(N^2 + 3N)a}. \]  

(A.10)

Thus, combining inequalities (A.9)-(A.11) with (A.8), we have proved (A.3).

If \{r_{l,m,n}\} is a three-dimensional sequence, the first-order differences of \{r_{l,m,n}\} with respect to \(l, m, n\) are defined by

\[
\Delta_l(r)_{l,m,n} = r_{l,m,n} - r_{l+1,m,n}, \\
\Delta_m(r)_{l,m,n} = r_{l,m,n} - r_{l,m+1,n}, \\
\Delta_n(r)_{l,m,n} = r_{l,m,n} - r_{l,m,n+1},
\]

respectively. The second-order differences of \{r_{l,m,n}\}, based on the first-order difference, are defined by, for example,

\[
\Delta^2_{ll}(r)_{l,m,n} = \Delta_l(r)_{l,m,n} - \Delta_l(r)_{l+1,m,n}, \\
\Delta^2_{lm}(r)_{l,m,n} = \Delta_l(r)_{l,m,n} - \Delta_l(r)_{l,m+1,n}, \\
\Delta^2_{ml}(r)_{l,m,n} = \Delta_m(r)_{l,m,n} - \Delta_m(r)_{l+1,m,n}.
\]

Higher order differences can be defined similarly.

\textbf{Lemma 2} (Abel's lemma) \textit{Let \{r_{l,m,n}\} be a three-dimensional non-negative sequence such that all first-order differences, second-order differences $\Delta^2_{mn}(r)_{l,m,n}$, $\Delta^2_{lm}(r)_{l,m,n}$, $\Delta^2_{ml}(r)_{l,m,n}$, and third-order difference $\Delta^3_{lmn}(r)_{l,m,n}$ of the sequence \{r_{l,m,n}\} are non-negative for all }\(l, m, n = 1, 2, 3, \ldots, \text{ and } \{b_n\}, \{c_n\}, \{d_n\} \text{ are three one-dimensional sequences such that their partial sums are bounded, i.e.,}

\[ \left| \sum_{n=n_0}^{n} b_i \right| \leq B, \quad \left| \sum_{n=n_0}^{n} c_i \right| \leq C, \quad \left| \sum_{n=n_0}^{n} d_i \right| \leq D \text{ for all } n \geq n_0 \geq 0. \]  

(A.12)
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Then, we have

$$\left| \sum_{l=l_0}^{l_1} \sum_{m=m_0}^{m_1} \sum_{n=n_0}^{n_1} r_{l,m,n} b_i c_m d_n \right| \leq r_{l_0,m_0,n_0} BCD \quad (A.13)$$

for all $l_1 \geq l_0 \geq 1$, $m_1 \geq m_0 \geq 1$, and $n_1 \geq n_0 \geq 1$.

Proof. We use notation $s_n(b)$ to denote the partial sum of a sequence $\{b_n\}$, i.e., $s_n(b) = \sum_{i=0}^{n} b_i$. Then, by Abel's transform on the sequence, we have

$$\left| \sum_{l=l_0}^{l_1} \sum_{m=m_0}^{m_1} \sum_{n=n_0}^{n_1} r_{l,m,n} b_i c_m d_n \right| = \left| s_{l_1}(b) \sum_{m=m_0}^{m_1} \sum_{n=n_0}^{n_1} r_{l_1,m,n} c_m d_n \right|
+ \sum_{l=l_0}^{l_1-1} s_l(b) \sum_{m=m_0}^{m_1} \sum_{n=n_0}^{n_1} \Delta_l(r)_{l,m,n} c_m d_n \right|
= \left| s_{l_1}(b) \{ s_{m_1}(c) \sum_{n=n_0}^{n_1} r_{l_1,m_1,n} d_n + \sum_{m=m_0}^{m_1-1} (s_m(c) \sum_{n=n_0}^{n_1} \Delta_m(r)_{l_1,m,n} d_n) \}
+ \sum_{l=l_0}^{l_1-1} s_l(b) \{ s_{m_3}(c) \sum_{n=n_0}^{n_1} \Delta_l(r)_{l,m_1,n} d_n + \sum_{m=m_0}^{m_1-1} (s_m(c) \sum_{n=n_0}^{n_1} \Delta^2_{lm}(r)_{l,m,n} d_n) \}\right|
= \left| s_{l_1}(b) \{ s_{n_1}(d) r_{l_1,m_1,n_1} + \sum_{n=n_0}^{n_1-1} s_n(d) \Delta_n(r)_{l_1,m_1,n} \}
+ \sum_{m=m_0}^{m_1-1} s_m(c) \{ s_{n_1}(d) \Delta_m(r)_{l_1,m_1,n_1} + \sum_{n=n_0}^{n_1-1} s_n(d) \Delta^2_{mn}(r)_{l_1,m,n} \}\}
+ \sum_{l=l_0}^{l_1-1} s_l(b) \{ s_{m_3}(c) \{ s_{n_1}(d) \Delta_l(r)_{l,m_1,n_1} + \sum_{n=n_0}^{n_1-1} s_n(d) \Delta^2_{lm}(r)_{l,m,n} \}\}
+ \sum_{m=m_0}^{m_1-1} s_m(c) \{ s_{n_1}(d) \Delta^2_{lm}(r)_{l,m_1,n_1} + \sum_{n=n_0}^{n_1-1} s_n(d) \Delta^3_{lmn}(r)_{l,m,n} \}\}
\leq BCD \left\{ \left| s_{l_1,m_1,n_1} + \sum_{n=n_0}^{n_1-1} \Delta_n(r)_{l_1,m_1,n_1} + \sum_{m=m_0}^{m_1-1} \Delta_m(r)_{l_1,m_1,n_1} \right| + \sum_{n=n_0}^{n_1-1} \sum_{l=l_0}^{l_1-1} \left\{ \left| \Delta_l(r)_{l,m_1,n_1} + \sum_{n=n_0}^{n_1-1} \Delta^2_{lm}(r)_{l,m_1,n} \right| + \sum_{m=m_0}^{m_1-1} \left| \Delta^2_{lm}(r)_{l,m,n} + \sum_{n=n_0}^{n_1-1} \Delta^3_{lmn}(r)_{l,m,n} \right| \right\} \right\}
= BCD \left\{ \left| r_{l_1,m_1,n_0} + \sum_{m=m_0}^{m_1-1} \Delta_m(r)_{l_1,m_1,n_0} \right| \right\}$
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$$\Delta_t(r_{l,m,n_0}) = \sum_{l=1}^{l_1-1} \left\{ \Delta_{l,m,n_0} + \sum_{m=m_0}^{m_1-1} \Delta_{l,m,n_0}^2 \right\}$$

$$= BCD\left(r_{l_1,m_0,n_0} + \sum_{l=1}^{l_1-1} \Delta_l(r_{l,m,n_0}) \right) = BCD r_{l_0,m_0,n_0}.$$ 

Now set

$$r_{l,m,n} = \frac{e^{-l^2+m^2+n^2}/4}{l^2 + m^2 + n^2}.$$ 

It is easy to verify that the three-dimensional sequence $\{r_{l,m,n}\}$ satisfies the conditions in Lemma 2. Let

$$b_l = \sin\left(\frac{l\pi}{2}\right) \sin(l\pi x) = \frac{1}{2} \left( \cos(l\pi (x - \frac{1}{2})) - \cos(l\pi (x + \frac{1}{2})) \right),$$

$$c_m = \sin\left(\frac{m\pi}{2}\right) \sin(m\pi y) = \frac{1}{2} \left( \cos(m\pi (y - \frac{1}{2})) - \cos(m\pi (y + \frac{1}{2})) \right),$$

$$d_n = \sin\left(\frac{n\pi}{2}\right) \sin(n\pi z) = \frac{1}{2} \left( \cos(n\pi (z - \frac{1}{2})) - \cos(n\pi (z + \frac{1}{2})) \right).$$

Since

$$\sum_{k=n_0}^{n} \cos(k\pi x) = \frac{\sin(n + \frac{1}{2})\pi x - \sin(n_0 - \frac{1}{2})\pi x}{2 \sin \frac{\pi x}{2}}$$

for all $n \geq n_0 \geq 0$, we have

$$\left| \sum_{k=n_0}^{n} b_k \right| \leq \frac{1}{\sin \pi (x - \frac{1}{2})}$$

for all $n \geq n_0 \geq 0$ and similar inequalities for the sequences $\{c_m\}$ and $\{d_n\}$. Thus, by Abel’s Lemma 2, we obtain

$$\left| \sum_{l=1}^{l_1} \sum_{m=m_0}^{m_1} \sum_{n=n_0}^{n_1} r_{l,m,n} b_l c_m d_n \right| \leq \frac{r_{l_0,m_0,n_0}}{\sin \pi (x - \frac{1}{2}) \sin \pi (y - \frac{1}{2}) \sin \pi (z - \frac{1}{2})}.$$ 

(A.14)

where $x, y, z$ are such that the denominator in the above inequality is not zero.

Now we give the estimation of the error $E(N, T_0)$. From formula (A.1) for $a_n$, it follows that

$$E(N, T_0) \leq \left| \sum_{l=1}^{\infty} \sum_{m=1}^{\infty} \sum_{n=1}^{\infty} r_{l,m,n} b_l c_m d_n - B_0(x, y, z) \right|$$
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\[
+3 \sum_{l=3}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} \frac{e^{-l_i,m,n}(\pi\sigma^2/4+\beta T_0)}{I_{l,m,n}} \\
+ \frac{8(2\sigma + \sqrt{\pi}/2)^3}{\pi^{9/2}\sigma^6} e^{-1/(4\sigma^2)} \sum_{l=0}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} \frac{1}{I_{l,m,n}(2l+1)(2m+1)(2n+1)} \\
= \left( \sum_{l=2N+1}^{\infty} \sum_{m=1}^{\infty} \sum_{n=1}^{\infty} r_{l,m,n} b_l c_m d_n \right) + \sum_{l=1}^{2N+1} \sum_{m=2N+2}^{\infty} \sum_{n=1}^{\infty} r_{l,m,n} b_l c_m d_n \\
+ \frac{8(2\sigma + \sqrt{\pi}/2)^3}{\pi^{9/2}\sigma^6} e^{-1/(4\sigma^2)} S.
\]  

(A.15)

Thus, from (A.2), (A.3) in Lemma 1 and (A.14), it follows that

\[
E(N, T_0) \leq \frac{3e^{-((2N+2)^2)x^2\sigma^2/4}}{\sin \pi(x - \frac{1}{2}) \sin \pi(y - \frac{1}{2}) \sin \pi(z - \frac{1}{2})} \frac{3}{((2N+2)^2 + 2)} \\
+ \frac{\sqrt{\pi}^3 + 8\pi\sqrt{((\pi\sigma/2)^2 + \beta T_0)} + 16\sqrt{\pi((\pi\sigma/2)^2 + \beta T_0)}}{4^4 \times 40((\pi\sigma/2)^2 + \beta T_0)^{3/2}} e^{-40((\pi\sigma/2)^2 + \beta T_0)} \\
+ \frac{24(2\sigma + \sqrt{\pi}/2)^3}{\pi^{9/2}\sigma^6} e^{-1/(4\sigma^2)}.
\]  

(A.16)

The above estimation for $E(N, T_0)$ is good only for those points $(x, y, z)$ when $\sin \pi(x - \frac{1}{2}) \sin \pi(y - \frac{1}{2}) \sin \pi(z - \frac{1}{2}) \neq 0$, otherwise, since

\[
\left| \sum_{l=1}^{\infty} \sum_{m=1}^{\infty} \sum_{n=1}^{\infty} r_{l,m,n} b_l c_m d_n - B_0(x, y, z) \right| \leq 3 \sum_{l=N+1}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} \frac{e^{-l_i,m,n}\pi^2\sigma^2/4}{I_{l,m,n}} \\
= 3S(N, \pi\sigma/2) \leq \frac{3((\sqrt{\pi})^3 + 4\pi^2\sigma + 4\pi^2\sqrt{\pi}\sigma^2}{32(N^2 + 3N)\pi^3\sigma^3} e^{-(N^2+3N)\pi^2\sigma^2},
\]

we have

\[
E(N, T_0) \leq \frac{3((\sqrt{\pi})^3 + 4\pi^2\sigma + 4\pi^2\sqrt{\pi}\sigma^2}{32(N^2 + 3N)\pi^3\sigma^3} e^{-(N^2+3N)\pi^2\sigma^2} \\
+ \frac{\sqrt{\pi}^3 + 8\pi\sqrt{((\pi\sigma/2)^2 + \beta T_0)} + 16\sqrt{\pi((\pi\sigma/2)^2 + \beta T_0)}}{4^4 \times 40((\pi\sigma/2)^2 + \beta T_0)^{3/2}} e^{-40((\pi\sigma/2)^2 + \beta T_0)} \\
+ \frac{24(2\sigma + \sqrt{\pi}/2)^3}{\pi^{9/2}\sigma^6} e^{-1/(4\sigma^2)}.
\]  

(A.17)

Therefore, we have proved
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Theorem 1

$$E(N, T_0) \leq E_0(N, T_0) + \frac{24(2\sigma + \sqrt{\pi}/2)^3}{\pi^{9/2}\sigma^6} e^{-1/(4\sigma^2)}$$

$$+ 3\sqrt{\pi}^3 + 8\pi\sqrt{(\pi\sigma/2)^2 + \beta T_0} + 16\sqrt{\pi((\pi\sigma/2)^2 + \beta T_0)} e^{-40((\pi\sigma/2)^2 + \beta T_0)}$$

where $E_0(N, T_0)$ is the smaller of

$$\frac{3(\sqrt{\pi})^3 + 4\pi^2\sigma + 4\pi^2 \sqrt{\pi}\sigma^2}{32(N^2 + 3N)^3\sigma^3} e^{-(N^2+3N)^2\sigma^2}$$

and

$$\frac{3e^{-(2N+2)^2\sigma^2/4}}{|\sin \pi(x - \frac{1}{2}) \sin \pi(y - \frac{1}{2}) \sin \pi(z - \frac{1}{2})||(2N + 2)^2 + 2|}.$$