Thermodynamics of Neurotransmission

Dissertation

zur Erlangung des Grades eines
Doktors der Naturwissenschaften

der Mathematisch-Naturwissenschaftlichen Fakultät
und
der Medizinischen Fakultät
der Eberhard-Karls-Universität Tübingen

vorgelegt
von

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2021

Tag der mündlichen Prüfung: ……27.04.2021……

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Abstract

There is a body of research mainly dedicated to study the means of temperature regulation in biological systems especially human body and how from small scale cells to to whole organ respond to temperature changes in the environment. This appropriate responses guarantee the maintenance of the condition under which, that biological system can function properly. Neural cells are no exception and their response perhaps requires a more precise measure because of their importance in a biological system.

All of that being said, the mechanisms by which neurons produce, use and propagate heat are not studied. The main topic of thesis is dedicated to study those mechanisms, specifically the dynamics of temperature within the synaptic cleft.

The transmission of neurotransmitters following release from pre-synaptic vesicles inside the synaptic cleft has been considered to be a diffusion process and its dynamics governed by Fick's laws. But other existing forces might contribute to propagation of neurotransmitters such as the electric fields of narrow synaptic clefts and temperature gradients. Since the experimental methods to observe the processes inside synaptic cleft is limited, we mainly rely on theoretical methods arising from statistical physics, thermodynamics and fluid dynamics to study these processes.

We use a non-equilibrium thermodynamic model which leads to system of partial differential equations that describes dynamics of temperature inside synaptic cleft. Finite element method (FEM) simulations, suggest that linear relationship between temperature changes and other factors such as number of release from binding sites also temperature difference between intracellular vesicles and extracellular synaptic cleft parts. The findings can provide a basis for temperature changes that are independent from those induced by blood flow and provide further factors to temperature change during short-term synaptic plasticity, long term potentiation or pathological conditions such as Epilepsy.

Contents

Chapter 1

Introduction

One of the challenges in neuroscience is to identify different processes in brain and try to find a measurable quantity which can characterize these processes. These processes range from fundamental microscopic activities such as neurotransmission, spiking, or opening of ion channels to macroscopic on-going activities such as blood-flow, macroscopic oscillations, brain waves and etc. Since the emergence of neuroscience as a field of study, scientists have developed experimental methods to target and measure the hypothetical quantities that could indicate and characterize the activity. For example, in order to measure the spiking of neurons, different electro-physiology methods such as patch-clamp have been invented. One can find similar developments for measuring macroscopic activities, as such for the blood-flow, the development of BOLD signal (Blood-Oxygen-Level-Dependent), which indicates the contrast between oxygenated and de-oxygenated blood, would tell us the increase or decrease of blood-flow in certain region.

In order to develop these measuring techniques, one has to be able to describe these processes with relevant physics. For example in case of spiking, we know that the main on-going activity has electrical nature. Opening of ion-channels would cause movement of charged ions through membrane and this would lead to the polarization of membrane and further generation and propagation of action potential. Polarization of membrane would tell us that by measuring membrane potential we can find out whether there is a spiking activity going on. But in order to fully understand that what measured values would tell us precisely about nature and stage of spiking, a mathematical formulation of whole processes is required. The propagation of electrical current through membrane and along neuronal axon can be formulated as an electrical circuit, having said that membrane's role is similar to a capacitor. Further description of processes has led people to development of cable theory in order to formulate whole activity.

Specifically speaking, previous theoretical studies of brain activity has mainly focused on electro-magnetic nature of spiking activity and relevant methods for measurement of spiking has been developed. But there are questions that simply cannot be answered by just looking at spiking and electrical activity of brain. These questions and cases include:

- If one is interested in some homogeneous measurement or indicator of activity, then spiking might not be suitable. The nature of spiking varies according to different cell types, different brain regions, different receptors and etc.[7].

- Spiking is locally measurable. It's almost impossible to get a whole-brain map of spik-

ing activities. Most state-of-the-art technologies of spike-recording (electro-physiology) can address at most several thousand sites at one electrode simultaneously [10], which is not sufficient in order to do a global measurement.

- In order to design complex behavioural experiments, it is not always necessary to look at activity of individual neurons. And even if we could, usually looking at spiking activity of individual neurons don't give us enough information correlate with designed stimulant or recorded behaviour [11].

In order to tackle these problems, scientist have developed different techniques to record a signal from brain which would indicate an on-going global activity. One of techniques which has been popular for almost two decades is called *functional magnetic resonance imaging* or *fMRI* in short. These technique of imaging mainly relies on measuring BOLD signal. BOLD signal correlates with the change ratio of Oxy-hemoglobin and Deoxy-hemoglobin (Oxygenated or Deoxygenated blood) that can be detected on the basis of their differential magnetic susceptibility[11]. Basis of this signal is glucose metabolism and one can see that nature of this signal is not directly related to electrical activity. BOLD signal shows less heterogeneity or sensitivity to which brain-region has been under study. It addresses activity in a bigger area which is called *Neurovascular Unit* and due to its dependence on metabolism, which its chemical reactions release or absorb well-defined amount of energy in form of heat, has thermodynamic nature. So far, BOLD signal has been successful in designing complex experiments and discovery of interesting patterns in brain activity. This motivates us, in order to try to dig further and look at different brain activities from a thermodynamic perspective.

We have already mentioned about thermodynamical nature of metabolism and therefore, BOLD signals. However, one can see that neurotransmission, which is the basis of spiking and propagation of action potential, is a diffusion process and diffusion process has also thermodynamical nature. Therefore one can hypothetically hope finding a connection between neural activity and BOLD signals through studying thermodynamical aspects of these processes and connecting them through *multi-scale*-wise.

In order to describe a system fully from a thermodynamical perspective, one needs to describe and quantify the thermodynamical variables which includes, volume (V), pressure (P) and temperature (T). Due to static nature of cells in brain and their lack of migration in after full development, usually has been assumed that brain functions in constant volume and pressure in different regions. For example pressure can be relevant in environments, where bulk flow and mechanical activity is present. Bulk flow is present in blood flow through vessels, but the moment they pass through *blood brain barrier* (BBB) the bulk flow translates into diffusion process. The difference between diffusion and bulk flow can be summarized as having directional movement. In bulk flow locally speaking, huge chunk of molecules have directional movement, whereas in diffusion such macroscopic behaviour is absent. Another example of presence of pressure dynamics would be developing organism, in which stress dynamics due to formation of tissues is present.[35] Therefore it would not make sense to try to measure and study dynamics of these variables. Temperature on the other hand, always have shown great variability from process to process and region to region in biology and we

hypothesize that brain is no exception. Reasons which makes temperature a good candidate for a fundamental variable to study throughout neuronal and biological processes are:

- Depending on technology for measuring temperature, it could be considered good candidate for a global measurement. Temperature is physically meaningful in different spatial and time scales, whether a neuron, brain region, neuronal firing or circadian rhythm. For any process of enough magnitude, temperature can be attributed. Whether this cannot be the case for specified activities such as electromagnetism.

- Temperature is scale-independent, since it's related to *average kinetic energy of molecules*, increasing or decreasing scale is not going to affect temperature's quantity or nature.

- Temperature is additive; if we can separate different processes generating heat in a system, their contribution to temperature of system would be additive. Therefore we can generalize from local (in time and space) temperature changes to global temperature changes. Though this addition, is not linear, but can incorporated in related heat diffusion equations.

- There are studies that shows association between clinical conditions with local or global temperature change in brain [12]. Therefore if one could describe pathological conditions in terms of molecular processes of different diseases such as epilepsy, measurable quantities such as temperature could help to localize and treat the condition.

There has been abundance of experimental methods and attempts in order to measure temperature changes in biological systems, and slowly scientists developing methods to apply these methods to central nervous system. As an example, development of nano-particles, nano-diamonds,gold-coating and so on, made it possible to measure temperature in from nano- to micro-scale.[13, 14]

As an example in [13], authors have used coating technique to coat Mitochondria with specific nano-diamond. The characteristic of nano-diamond is that if it receives a laser pulse, the radiated beam's wavelength is sensitive to very small temperature changes and from measuring its wavelength one can detect how much temperature changes during process of delivering and receiving pulse. Therefore, since Mitochondria works as an engine to transport molecules from soma of the cell to its dendrites, it moves from soma to dendrite. Therefore, if during movement of coated Mitochondria, we receive pulses with different wavelength, one could claim on-going temperature changes. Therefore, from recorded data, authors has concluded there must be temperature difference, around 1.5 Kelvin, between soma and dendrite of neuronal cells, due to detected temperature difference from moving coated Mitochondria. Other experiments in this area, has similar nature of coating specific molecules with nano-diamonds or similar molecules which their radiated pulse is sensitive to temperature and they design experiment to in a way, so that they could navigate and detect temperature changes during specific processes, either is going on spatially or time-wise or both.

Therefore it seems that there are technological availability for measuring temperature and the body of research in order make technology more precise and efficient, in terms of measure-

ment unit, time and spatiality to make it more suitable for small temperature measurements which is usually the case in biology and neuroscience. The question now remains is there any studies done for prediction of temperature changes in context of neuroscience?

There has been plenty of research to study the impact of temperature change *on* activity of synapses or a particular brain region [15, 16, 17]. But vice versa, studying the temperature change or the on-going dynamic on temperature, has barely given attention. It is a widely accepted fact that blood flow has the role to regulate temperature. Accordingly, main seminal study which can be found as a starting point to measure temperature changes due to brain activity, is Yablonskiy's seminal study and therein he tries to use the idea that blood flow also regulates local brain temperature [18].

He argues that heat in brain is mostly generated by oxygen consumption and glucose metabolism. In resting state this heat generated by oxygen consumption is removed by blood and as a result brain temperature also remains steady. But major functional activity can change the blood flow to a region and as a result disturb the balance and change the temperature. And more blood flow to a region or to a neurovascular unit can lower the temperature. The temperature change in this region due to blood flow might also propagate to neighbouring area due to diffusing nature of heat. Therefore dynamics of temperature change overall can be predicted from heat equation, with considering source (blood flow) and diffusion.

Accordingly, the line of reasoning to fully describe the model for temperature changes goes like this:

- Most of the energy required for brain activity is released from oxygen and glucose reaction, at 37°C, is: $glucose + 6O_2 \rightarrow 6CO_2 + 6H_2O$, released $\Delta H_\circ = 470kJ$ enthalpy per mol of O_2

- Almost all of this energy is being dissipated as heat.
- Some portion of released heat namely, ΔH_b, used in a reaction to release oxygen from Hemoglobin.
- Q_r^+ Heat released per gram of tissue per minute: $Q_r^+ = (\Delta H^\circ - \Delta H_b) \cdot rCMRO_2$, $rCMRO_2$: regional cerebral metabolic rate of oxygen, on average, $15\mu \cdot mol \cdot g^{-1} \cdot \min^{-1}$, and $\Delta H_b = 28kJ$ on average.
- Rate of heat removal by blood flow, $Q_r^- = rCBF \cdot \rho_B \cdot C_B \cdot (T - T_{artertial})$, $rCBF$: regional cerebral blood flow, ρ_B: blood density, C_B: Cerebral heat capacity.
- Using Penne's bio-heat equation one can describe the total dynamics of temperature distribution caused by local changes in blood-flow and oxygen consumption. We would have:

$$C_{tissue} \cdot \dot{T} = (\Delta H^\circ - \Delta H_b) \cdot rCMRO_2 - rCBF \cdot \rho_B \cdot C_B \cdot (T - T_{artertial}) \qquad (1.1)$$

which $C_{tissue}$is the heat capacity of tissue.

After, coming up with equation for describing the dynamics of temperature change in a neurovascular unit, he goes on explain that how one can detect local brain temperature changes from *fMRI signal*. The frequency of fMRI signal is temperature dependant. The whole equation which accordingly would describe the dependency of fMRI signal to temperature change is:

$$\Delta R_2 = \frac{0.4\pi}{3} \cdot \log Q_{10}\gamma \cdot B_0 \cdot \Delta\chi_0 \cdot (1 - sO_2) \cdot \zeta \cdot \Delta T. \tag{1.2}$$

$$\tag{1.3}$$

whichΔR_2 denotes the changes in R_2 relaxation rate constant.

In following research [19], Yablonskiy improved model in order to consider the difference between dynamics of temperature change in areas closer to brain surface and deep brain structure. Apparently, temperature in deep brain structure is higher than temperature of arterial blood and situation is vice versa in areas closer to brain surface due to exchange of heat with environment[19]. First they idealize the dynamics accordingly so they can have a heat diffusion equation for total temperature distribution:

$$K \cdot \nabla^2 T + Q - Q_r = 0 \tag{1.4}$$

Where $Q = (\Delta H^\circ - \Delta H_b) \cdot [O_2] \cdot \rho F \cdot OEF$ is the heat generated by metabolic process and $[O_2]$ is the concentration of oxygen in blood and OEF is the oxygen extraction fraction. And Q_r is the heat removed by blood.

Therefore considering this heat equation, which one has to solve in a specific and well defined geometry, author argues that, considering the *characteristic length* of the equation, what would be the dynamics of the temperature compared to baseline problem. The baseline problem would be solving the equation in resting state where $Q = Q_r$ and its solution is shown by notation $T_0(r)$. And arguably the the fluctuation of temperature from $T_0(r)$ is going to be different depending on location of region and its distance from surface.

In same year, Yablonskiy [20], with collaboration of colleagues, conducted experiments to investigate experimental basis for theoretical research suggested above. They used *thermocouple probes* to measure temperature in different depths of brain and their experimental results suggests the different dynamics of temperature change correlated with brain depth and related parameters.

Summarizing the Yablonskiy's research in mentioned articles, they were trying to model dynamics of temperature due to blood flow and metabolism in brain. This phenomenon

mainly can be studied in scale of neurovascular unit, which mathematically translates to approximately several micro-meter and time scale which takes for blood to regulate the temperature, approximately several seconds.

There are other studies which came after Yablonskiy's seminal work, all studies related to study temperature dynamics in a certain clinical condition [14, 16, 22]. The basis of almost all of these studies is Penn's *Bio-heat equation* [21], which basically relates the *Laplacian* of temperature to sources of heat in a biological system in the cases of studies mentioned before, their source of heat removal and generation all comes down to blood flow and metabolism. Depending on the question they want to answer, their modify the *boundary conditions* and *initial values* of the Bio-heat equation to find a solution for that question or an approximation of that.

Yablonskiy's model might describe the spatial temperature changes due to blood-flow, but is going to ignore the other sources of temperature changes due to heat dissipation, or other hydrodynamical processes that might occur in smaller spatial or temporal scales such as synapse. So our mission in this thesis would be mainly to focus on such sources of temperature, which seems to be fundamental. Before explaining further our idea of temperature change in synapse, since we need a complete description of total dynamics of neurotransmitter diffusion, we might consider other events that has been ignored before such as electro-diffusion or in other words contribution of existing electrical fields in synapse to neurotransmitter movements.

Not until recently, the effect of existing electrical field on movement of neurotransmitter in synapse has been neglected. The main assumption so far about movement of molecules and particles during processes such as neurotransmission or ion-channel opening, has been the the existing concentration gradient, that particles moving from one place to another, where concentration is lower. But we know that there is going to be an electrical field in synaptic cleft due to to difference between membrane potential of pre- and post-synaptic neuron and this difference is going to cause an emergence of an electrical field in that region. Movement of charged neurotransmitters like glutamate is affected by this. Similar can be said about dipole neurotransmitters.

Before going into detail how we can import this effect in our modelling (equations arising from non-equilibrium thermodynamics as we will see in next chapters), we are going to review studies done on this phenomenon. But before digging deeper in this issue, naturally the question arises that why determining effect of electrical field on mechanisms of diffusion would be question worthy of answer? The reason is the time course of neurotransmitter in synaptic cleft, contributes to the kinetics of the post-synaptic current as well as determines the rate of escape from the cleft. In fact, extra-synaptic actions of neurotransmitters have recently emerged as an important mechanism in regulating transmission at central glutamatergic synapses. Therefore It would be logical to believe that the mechanisms controlling diffusion of neurotransmitter in the cleft have an immediate impact on temporal and spatial integration of synaptic signalling [6, 31].

The main seminal work, which has suggested significant effect of *electro-diffusion* on neurotransmission is done by Rusakov and Schevteschenkov [6]. First, they consider existence of electrical field generated by electrical current, carried by AMPA on post-synaptic neuron coming from synaptic cleft. Therefore, they form an electro-diffusion equation in polar coordinates in the form below:

$$\frac{\partial c}{\partial t} = D\Big(\frac{1}{r}\frac{\partial}{\partial r}r(\frac{\partial c}{\partial r}) + \frac{qF}{RT}\frac{1}{r}\frac{\partial}{\partial r}r(c\frac{\partial V}{\partial r})\Big) \tag{1.5}$$

V here is the synaptic cleft's voltage and F denotes the Faraday constant The post-synaptic current I_{syn} through the open receptor channels is due to the flow of ions through the narrow synaptic cleft. This causes a radial voltage drop (it is assumed that AMPA receptors mainly concentrated in middle of synapse, therefore spherial coordinates indicating voltage drop away from this area has been used in this modelling), so that the potential in synaptic cleft follows the equation:

$$\Psi_m\frac{\partial V}{\partial t} = \frac{h}{R_{ex}}\Big(\frac{\partial^2 V}{\partial r^2} + \frac{1}{r}\frac{\partial V}{\partial r}\Big) - \frac{I_{syn}}{2\pi\rho_\alpha}\delta(r-\rho_\alpha) \tag{1.6}$$

ρ_α here indicates the small region's radius, where AMPA receptors are located, R_{ex} is the synaptic cleft's specific resistance and Ψ_m is the specific capacitance of the post-synaptic membrane. Considering these two equations and the fact that electrical field is the spatial derivative of the potential, due to nature of electrical fields in this investigation, its solution outside of receptor zone ($r > \rho_\alpha$), is:

$$E(r) = \frac{dV}{dr} = \frac{I_{syn}R_{ex}}{2\pi hr} \tag{1.7}$$

where $h = 15nm$ is the height of synaptic cleft. With some estimations coming from authors, these yields approximation of $E \approx 2\times 10^4\frac{V}{m}$ in this region.

Forming boundary conditions and all that, they provide analytical solution for concentration profile. This analytical solution is comprised of two parts: one describe time course of concentration due to *free diffusion* and the other term the effect of *electro-diffusion*. The effect of electro-diffusion depends on characteristic number K, which this number comes from nature of neurotransmitter and its charge (negative or positive or zero in the case of no charged neurotransmitter therefore no electro-diffusion).

According to their study at $K = 0.1$, which is the case for glutamate, could speed up its clearance, 4-5 ms post-release, by up to 50 percent. Authors also conclude that interaction of negatively charged glutamate with an inward current ($K > 0$) would contribute to reduction of synaptic receptor responses, whereas outward current, should slow down the glutamate clearance from the cleft and thus enhance the receptor activation.

In a following study, authors conduct experiments to study the effects of electro-diffusion on excitatory transmission. [31] They investigated the effect of electro-diffusion of excitatory post-synaptic currents (EPSC), average glutamate synaptic clearance time and in general

glutamate diffusion. For example, they observed greater dwell time of glutamate in synaptic cleft at positive than at negative voltages.

Accordingly we can see that electro-diffusion, which deemed to be negligible before, has significant consequences on synaptic processes from movement of neurotransmitters to their clearance from cleft. This changes in microscopic scales can have significant effect on behaviour of large-scale neural networks. We will later on use slightly different approach for incorporating electrical field emerged from charged neurotransmitter with mass-heat diffusion, instead of looking at synaptic currents.

Now we can continue explaining our approach. In almost all of the previous studies, the focus was on modelling and measuring temperature changes due to blood flow and metabolism. But there are other processes in brain which could contribute to temperature changes, heat generation or heat absorption. In order to, dig deeper, we want to have a basic understanding of temperature changes, which is not caused by blood flow or metabolism. One of the most fundamental brain activities which one can attest is the basis of information processing in our brain, is spiking. There are different ways which neurons use to propagate or generate spiking, which among them we mainly know of synaptic junctions and synaptic neurotransmission [7]. Almost 80 percent of all spiking events are transmitted by neurotransmission. **Since we are trying to look at different brain processes from thermodynamic perspective, therefore it would make sense try to understand the thermodynamics of this action, mainly dynamics of temperature during neurotransmission.**

During neurotransmission, neurotransmitters are released from pre-synaptic neurons, at different synapses and they make their way by diffusion[7] to post-synaptic neuron. When they reach membrane of post-synaptic neurons, they bind to neuro-receptors. Depending on neurotransmitter and type of receptor they bind to, they cause generation of action potential in post-synaptic neuron, either by way of directly opening the ion-channel pores (*Ionotropic receptors*) or by way of complex pathway which uses *Second Messengers* to open the ion channels(*Metabotropic receptors*). These are called *excitatory synapses*. There is other type of synapse in which neurotransmission causes post-synaptic neuron to less likely generate action potential. These are called *inhibitory synapse*.

In either case, the main transmission happens in synaptic cleft, where the neurotransmitters diffuse after being released from synaptic vesicles. The release of neurotransmitters and their binding to post-synaptic neuron causes ion flow through post-synaptic membrane and results in small changes of post-synaptic neuron potential which are called *Excitatory postsynaptic potential (EPSP)*. By generating more EPSP, neuron is more likely to generate action potential. So detecting any electrical activity from post-synaptic neuron is caused by neurotransmission events, whether EPSP, or action potentials themselves. Therefore, studying neurotransmission is always helpful to understanding general electrical activities.

In our case, we are interested in temperature changes. *Can neurotransmission lead to temperature changes?* In order to answer this question, which is going to be the central theme of this thesis, we have to look at the events going on in synaptic cleft, since spatially the

main process of neurotransmission is happening there. For the sake of simplicity, we focus mainly on excitatory synapses. Another simplification we might want to take is that, we assume we are working with one neurotransmitter at one synapse. Though this might be not realistic, but would capture the main question we are trying to answer and that is *how temperature fluctuations will be propagated with diffusion.* In later studies, one can add several neurotransmitters to form more complicated coupled diffusion dynamics, which would require more computational powers to study them numerically. But at this point and at the level of testing this idea, this deems huge and unnecessary.

Synaptic cleft is very narrow, with height of approximately 15-50 nm. There are also mathematical studies, in order to find the optimal height of synaptic cleft, which is calculated to be almost 20 nm [9]. We fixate on this value for simplicity as the height of synaptic cleft. Considering our assumption, one can say that neurotransmission occurs in spatially mesoscopic to microscopic scale. Therefore, *hydrodynamic limits*, would tell us that, though a specific neurotransmitter could be considered solid in macroscopic scale, but in our problem we can safely assume that neurotransmission is basically mixture two fluids in mesoscopic scale. Behaviour of fluid in macroscopic scale, is defined as a material which is prone to flow under stress. Similar definition, which covers almost any spatial scale, would define liquid/fluid as lacking long-range interaction, which possessing short-range interactions. The very assumption, which underlies the diffusibility of neurotransmitter complies with these definitions. In previous studies, where they assume neurotransmission is a diffusion process and propagate under *fick's second law*, also conforms to this idea. [7]

Before, the release, the neurotransmitters are confined and compacted in *synaptic vesicles* along with possible molecules such as water and salt and they have small mean free path. After release, the entropy of whole system (considering both neurotransmitters and extracellular fluid in synaptic vesicle) increases and they have in increase in mobility and mean free path. Therefore, according to thermodynamics, one can assume there is going to be heat generation in system and therefore increase in temperature. Simply from formula[23]:

$$\Delta S = \int_i^f \frac{dq_{rev}}{T}, \tag{1.8}$$

which tells us the relation between change in entropy and reversible heat transfer release, one can see the relation between heat generation and entropy. This simple intuition from the mathematical and physical nature of neurotransmission, motivates us to go deeper in modelling the synaptic transmission and see how the temperature dynamics is going be like.

Before going further, in Figure 1, we explain the sketch of thesis and how can be followed depending on interested reader.

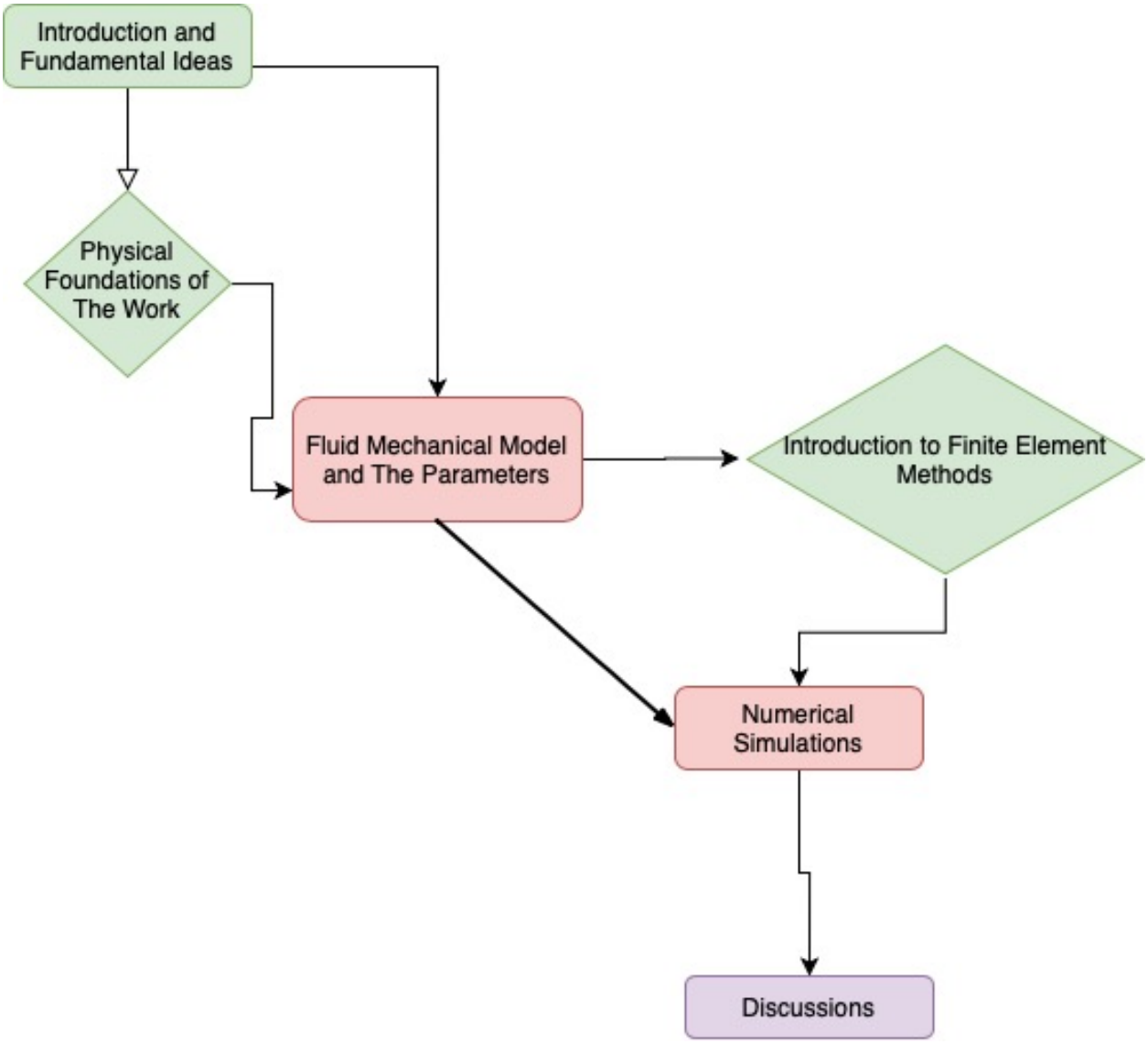

Figure 1: A scheme of the thesis. The arrows shows the prerequisites of of chapters and how they can be followed. Depending on reader, one can jump to main results in violet sections, if one already has the background.

We already covered the introduction to the thesis. One can already jump to equations in **Multi-Physics model and parameters** section and further to **Numerical simulations** for further results arising from simulating partial differential equations arising from our model. Green parts in the sketch provide the methods that we used for our work. In next subsection, we give an introduction about the how to define temperature and what is the appropriate physics for modelling the temperature dynamics at synaptic cleft.

1.1 Fundamentals of Temperature

Before, trying to choose our methods for modelling the neurotransmission, the most basic question which has to be answered is: *What is Temperature?*

For humans, the concept of temperature has been always around, since we have a sense of hot and cold. Even though the sense of hot and cold mainly depends on flux of heat through our skin rather than the actual temperature of the environment that we're in. Before theoretical foundation of statistical mechanics has been established, several methods and devices for measuring of temperature has been invented. For example, *Celsius*, which the measure is based on dividing temperature between boiling point and freezing point of water, in 100. So the idea was finding two constant points (hopefully assumed to be constant), by help of them try to find a metric to measure temperature [24].

With the emergence of statistical mechanics and since we know that everything is made of particles, the question arises that how one could temperature, as a thermodynamic property, could be related to the particles, which our system of study is consisted of them? The first approach by, Daniel Bernoulli, was to compute this relation for ideal gases. Later people could show that, if an ideal gas is made of particles of mass m, therefore we would have following for temperature [23]:

$$m < v^2 >= k_B T \tag{1.9}$$

Physical interpretation of this formula would be that temperature is basically *average kinetic energy of molecules in the system.* Since we are talking about averages and all that, therefore speaking of temperature of single molecule would be meaningless. In general, the formula above would not be correct for all systems of study, since collision and interaction between molecules, which is neglected in ideal gas makes properties of system more complex to have simple formula for temperature.

In statistical mechanics, the introduction of probabilistic interpretation on particle's coordinates has been revolutionary. The idea is that, if we are dealing with a system with many particles, in order to fully describe this system according to *Newtonian Mechanics*, we need the spatial coordinates plus their momentum. If we have N particle in our system, this would give us $3N+3N = 6N$ numbers. If we have initial values of these $6N$ numbers, putting them in differential equations which arise from interpreting Newton's laws and solving them, would give us coordinate and momentum of particles in other time steps. But the the problem is that, solving these number of differential equations is computationally infeasible. And even if we could, is it really necessary? Or we can describe system with less parameters efficiently?

The relation between macroscopic and microscopic state of system is not one-to-one. In fact there are many microscopic states of a system, which would give us the same macroscopic state. For example, as we found out, we think of temperature as mean kinetic energy of the particles, there are many microscopic states which would give us the same temperature. Mathematically speaking, if we have N particles, therefore particles which have their

sum of squared velocity is constant(in ideal gas), i,e:

$$v_1^2 + ... + v_N^2 = Const. \tag{1.10}$$

They are going to have same temperature. The equation above is in fact have infinite solution and their solution give rise to $N-$dimensional sphere. This leads to define the concept of *ensemble* which is the collection of microscopic states, sharing same set of macroscopic properties. The concept of ensemble, is very similar to foundations of *probability theory*). One has to define the mathematical concept of ensemble in following way:

If we denote, *ensemble distribution function* $f(x,t)$, this distribution function has the property that $f(x,t)dx$ is the fraction of total ensemble members contained in phase space volume dx at time t (phase space is the space of coordinates and momentum for N particles which would give us a $6N$ dimensional space) and

$$f(x,t) \geq 0 \tag{1.11}$$

$$\int dx f(x,t) = 1 \tag{1.12}$$

Therefore $f(x,t)$ is a probability density. The first problem that appears is that, $f(x_t,t)dx_t$ should be time-independent so we can have a useful integration. Fortunately *Liouville's Equation* provides us with the property we want, which states $dx_t = dx_0$ and $\frac{df}{dt} = 0$ and would result in $f(x_t,t) = f(x_0,0)$, therefore we have:

$$f(x_t,t)dx_t = f(x_0,0)dx_0 \tag{1.13}$$

Using Lioville's Equation, we can if have an observable $a(x)$ for a macroscopic variable A, then:

$$A =< a(x) >= \int dx f(x,t)a(x) \tag{1.14}$$

Therefore, depending on the ensemble we have, for the macroscopic variable A, we can find out what is the observable $a(x)$ and calculate A. A consequence of Liouville's equation is that, if Hamiltonian of our system is defined by $H(x)$, we would have:

$$\frac{\partial}{\partial t} f(x,t) + \Big\{ f(x,t), H(x,t) \Big\} = 0 \tag{1.15}$$

where $\Big\{ .., .. \Big\}$ is called *Poisson Bracket* and defined by:

$$\Big\{ a, b \Big\} = \sum_{\alpha=1}^{3N} \Big[\frac{\partial a}{\partial q_\alpha} \frac{\partial b}{\partial p_\alpha} - \frac{\partial a}{\partial p_\alpha} \frac{\partial b}{\partial q_\alpha} \Big] \tag{1.16}$$

If A is a *thermodynamic equilibrium* observer, therefore its integral should be time-independent and this happens when $\frac{\partial f}{\partial t} = 0$. In this case equation 1.16 is going be simplified to:

$$\Big\{ f, H \Big\} = 0 \tag{1.17}$$

Therefore f must be a function of Hamiltonian, i,e:

$$f \propto F(H(x)) \tag{1.18}$$

We know that if a system obeying Hamilton's equations conserves the total Hamiltonian $H(x) = E$, where E is the total energy of the system. Therefore total energy of an ensemble should be constant for a system under Hamiltonian dynamics. Therefore we must have:

$$F(H(x)) = M\delta(H(x) - E) \tag{1.19}$$

where δ denotes *Dirac's δ function* and M is the normalization factor. This form of ensemble is called *Microcanonical Ensemble* and for an observer A the calculation goes like this:

$$A =< a(x) >= \frac{\int dx a(x)\delta(H(x) - E)}{\int dx \delta(H(x) - E)} \tag{1.20}$$

We are interested in having the measure for temperature and *classical viral theorem* provides us with that information.

$$\left\langle x_i \frac{\partial H}{\partial x_j} \right\rangle = kT\delta_{ij} \tag{1.21}$$

where average is taken with respect to a microcanonical ensemble and k here denotes Boltzmann constant. Hereby we have an analytical way to calculate temperature from microscopic states of the system, by means of having a probability distribution over them. So we have the phase state function $a(x) = x_i \frac{\partial H}{\partial x_j}$ defined for temperature. If we have the full description of $f(x, t)$, we can calculate temperature. Overall what have calculated and defined, is going to be a bit different in a system which is *non-equilibrium thermodynamic state*.

Furthermore, if we consider $f(x, t)$ to be our ensemble or distribution function again, it is not easy to solve describe this function comprehensively again. If we have one mole of particles in our system, then there this function would have 10^{23} variables. Dealing with such a function is computationally infeasible.

We can simplify the problem in following way: instead of trying to describe a probability distribution for all of the particles in system, we come up with a probability distribution which would give us *probability of finding particles in certain position.* It is called *one-particles distribution function* and it captures number of particles lying at some point $x = (r, p)$ in coordinate space(r here denotes the coordinates for location and p coordinates for momentum). It is defined by [25] :

$$f_1(x, t) = N \int \prod_{i=2}^{N} dx_i f(x, x_2, x_3, ...x_N; t) \tag{1.22}$$

Calculating further to find out about dynamics of $f_1(x, t)$, we would come up with so called **Boltzmann Equation**:

$$\frac{\partial f_1}{\partial t} + \dot{x} \cdot \nabla_x f_1 = \left(\frac{\partial f_1}{\partial t}\right)_{coll} \tag{1.23}$$

$\left(\frac{\partial f_1}{\partial t}\right)_{coll}$ is called collision term and states that how this probability distribution is affected by collision between particles. Throughout different research and problems, people have defined different collision term for the problem. The original collision term which Boltzmann came up with is:

$$\left(\frac{\partial f_1}{\partial t}\right)_{coll} = \int d^3p_2 d^3p_1' d^3p_2' w(p_1', p_2'|p, p_2)\Big[f_1(r, p_1')f_1(r, p_2') - f_1(r, p)f_1(r, p_2)\Big] \tag{1.24}$$

w, here denotes the collision rate kernel. So as we can see, Boltzmann Equation is a *integro-differential equation* which is also non-linear. This makes it very hard to solve analytically and in fact is open problem.

Trying to solve Boltzmann Equation numerically has led researchers to discover *Lattice Boltzmann Methods* (LBM) [26]. The main idea of Lattice Boltzmann method is that, first we discretize space into lattices and we assume particles are located on these lattices. The lattice could have many shapes, depending on degree of freedom we want to give to the particles. We also discretize time coordinates and each time step we update the movement and location of particles with respect to Boltzmann equation. Therefore in a basic Lattice Boltzmann algorithm there two steps of *collision* and *streaming*.

For example, if our space is discretized according to lattice, therefore movement of particles is limited to set of vectors $\Big\{e_0, e_1, e_2, ...e_8\Big\}$ in which e_0 indicate no movement in next time step. In that case. Collision state is update according to *BGK equation* which is summarized below:

$$f_i(x, t + \delta_t) = f_i(x, t) + \frac{f_i^{eq}(x, t) - f_i(x, t)}{\tau_f} \tag{1.25}$$

$f_i(x, t)$ here indicates density of particle at lattice point $i \in \Big\{0, 1, 2, .., 8\Big\}$ and $f_i^{eq}(x, t)$ is the equilibrium density along direction i.The model assumes that the fluid locally relaxes to equilibrium over a characteristic time-scale τ_f. Streaming step is updated like below:

$$f_i(x + e_i, t + 1) = f_i(x, t) \tag{1.26}$$

After doing collision and streaming steps one can retain macroscopic hydrodynamical quantities from *Chapman-Enskog Expansions* which relates quantities such as bulk velocity to mesoscopic quantities of ensemble density functions through integro-differential equations. A basic LBM algorithm can be summarized below:

Algorithm 1: A LBM Algorithm

```
Initialize Lattice, Geometry, relaxations time and related parameters;
while As long as needed do
    Update Collisions;
    Update Streaming;
    Apply boundary conditions ;
    Calculate macroscopic quantities according to Chapman-Enskog ;
    Calculate bulk and equilibrium velocity;
    Update time and number of steps;
end
Post-Processing
```

The dynamics chosen between streaming and collision, that is going to happen in next step is according to certain probability measures. Solving LBM equations requires massive parallel computing. But more importantly can we apply it to our question? The answer is for now could be negative, since research on tailoring LBM in order to work for *miscible mixtures* still continues and certainly not for non-equilibrium case. The reason is that defining $f_i^{eq}(x,t)$ requires to temperature to be considered **constant** and in other case, would cause complexities that LBM cannot handle. Therefore after giving introduction to concept of temperature and how we can we find numerical ways to solve equations, which approximate true theoretical value of temperature, now we have to move on for other theoretical methods to find a way to model temperature.

Also if we wanted to look at temperature from macroscopic perspective, *the inelastic collision between molecules*, would cause dissipation of heat and as a result change in temperature. But if we neglected this and assume this is negligible, therefore instead of trying to look at temperature from down to top, let's say in Boltzmann equation, we can go top to down and just look at what happens to temperature in other scales. One can probably claim that this two approach would converge to each other if we neglected heat generation due to collision of molecules, which is naturally included in derivations of Boltzmann equation. Before diving into more macroscopic treatment of temperature, we would point out to other sources of temperature changes.

- We already talked about how inelastic collision between molecules contribute to temperature change. In order to compute this we have to consider the fact this would happen in the case the two molecules have different properties and mass. If we treat two molecules as two objects in *Newtonian Mechanics*, we know that their collision with each other is going to change the their total kinetic profile. Going from Newtonian Mechanics to Statistical Mechanics, we know intuitively that, temperature reflected average kinetic energy of molecules. That would be reflected in the Hamiltonian of the system and therefore according to *Classical Virial Theorem*, this would lead to change in temperature's value. One way to compute this would be solving Boltzmann Equation and finding the ensemble and finally computing temperature. We already discussed previously how state of the art numerical algorithms cannot handle this.

Another approach would be using *Molecular Dynamics*, which the the basic algorithm can be summarized below:

Algorithm 2: A Molecular Dynamics Algorithm

Acceleration $a = 0.0$, time $t = 0.0$, $i = 0$ and time-step Δt
Initialize location $r_{i=}$ and velocity $v_{i=0}$ at step $i = 0$;
while *As long as needed* **do**
  Update velocity and locations:
  $r_i = r_i + v_i \Delta t + \frac{1}{2}\Delta t^2 +$ higher order terms
  $v_i = v_i + a\Delta t +$ higher order terms;
  Update Forces: $F = F(\Psi(r_0))$ $a = \frac{F}{m}$;
  Update locations and velocity based one new a;
  Apply boundary conditions ;
  Calculate macroscopical quantities of interest ;
  Update time and number of steps ;
end

In Molecular dynamics, we treat molecules as if they are in real objects of study in Newtonian Mechanics and therefore we have to solve equations according to classical mechanics to get what we want. Molecular dynamics (MD) computations although are very intensive, with powerful computing systems it is feasible to do this computations up to nearly 10^8 particles in system. Nevertheless, if we wanted to use MD to calculate temperature change due to inelastic collision, we had to approximate temperature change to be average difference in kinetic profile our system during the process. Even though, for sake of simplicity, we say that temperature reflects the average kinetic profile, but mathematically speaking it is just an intuition for Classical Virial Theorem, which is a calculation of *Expectation* of a function, with probability distribution, which in our case is Micro-canonical Ensemble. Therefore our calculations from MD, just reflects an approximation of this, which we don't know how reliable is this approximation. Therefore, doing this intensive task for just getting an approximation of negligible quantity does not make sense and as a result we neglect this source of temperature.

- Second source of temperature change in synaptic cleft during neurotransmission could from mixing two sources of particles with different temperature. If we assume neurotransmitters which are coming from intracellular space, and extracellular matrix in synaptic cleft have different temperatures, therefore during neurotransmission, the temperature in synaptic cleft has to change. The precise dynamics of this source of temperature is predictable from *Penne* alike equations, which we talked in introduction and previous works on temperature studies. This form of temperature source is meso- to macroscopic and basis for that would be *heat diffusion equation.* This source of temperature, would considered in general framework, which we would later talk about and that is *non-equilibrium thermodynamics.*

- When we were talking about motivations for studying temperature in synaptic cleft, we

said that since neurotransmitters are confined in compact space and after release they go to bigger space and their entropy therefore increases and accordingly this could lead to heat generation. This source of temperature is also computable from basic of statistical mechanics, since definition of entropy and temperature is very interrelated. But also the framework of *non-equilibrium thermodynamics*, would predict temperature change due to this source as well and we will come it.

- when neurotransmitters are released, a percentage of them degrade due to enzymatic reactions in synaptic cleft. This chemical reactions could generate or absorb heat and we will come back to this term and see how we can input it in *partial differential equations* arising from our framework.

- Another source of temperature is *thermodynamic fluctuations*, which sort of acts as uncertainty in deterministic hydrodynamic equations, which arise from random thermal movement of molecules. Incorporating thermal noise in simpler equations such as diffusion equation is well-studied. But adding them to our highly non-linear equations, as we will see later, would require a more comprehensive modelling which is out of scope of this thesis and can be delegated to a prospect research.

Now we are ready to start with theory of *non-equilibrium thermodynamics* and our modelling of the problem at hand.

Chapter 2

Physical Methods

2.1 Non-equilibrium Thermodynamics

In this section we review basics of non-equilibrium thermodynamics and how we derive equations for binary mixture based on non-equilibrium thermodynamic principles and continuity assumptions. For advanced readers, we suggest to refer to [1].

In previous chapters we noted what does *thermodynamic equilibrium* mean. A system or a subsystem is said to be in thermodynamic equilibrium if the fundamental thermodynamic variables would not change through time if it is isolated from its environment. The fundamental thermodynamic variables can be summarized in Temperature, T, Pressure, P, and Volume V. The other variables are functions of these variables.

Characteristic functions define the relationships between fundamental thermodynamic variables and the other ones. For example entropy function S, upon differentiation to fundamental variables leads to other variables such as heat capacity and so on. An equation of state describes relationship between pressure, temperature and density, which they are the variables describe a thermodynamic system thoroughly. One of the main relationship between thermodynamic variables is of the form:

$$d\rho = \rho[\delta_T dp - \alpha_p dT] \tag{2.1}$$

where ρ is mass density, p pressure, T Temperature, δ_T isothermal compressibility and α_T thermal expansion coefficient. We will extend this equation of state to general non-equilibrium case in next chapters.

2.2 Assumptions of Non-equilibrium Thermodynamics

In order to study thermodynamic non-equilibrium systems, we have to restrict and simplify the case in order to be able find some patterns. If system is really far from equilibrium and chaotic, therefore it would be impossible to track the dynamics of the system. *Therefore we assume that our system of study is not far from equilibrium and reaches equilibrium pretty fast.*

The first assumption about systems which are not far from equilibrium is that they "locally" behave like a system in thermodynamic equilibrium. If we consider a small volume

in system it is going to be in thermodynamic equilibrium and its thermodynamic variables is going satisfy certain conditions. Mathematically speaking, this lead to assume that equations of state in thermodynamic equilibrium is going to be extended as a function of time and space to be satisfy the "locality" condition in thermodynamic non-equilibrium system. For example, In thermodynamic equilibrium we had the equation of state which described a relationship between pressure, temperature and density. That equation of state therefore was globally true for that system. Here since we have local equilibrium we our equation of state can true locally, and for every coordinate in time and space we can attribute an equation of state. If we extend this to be a local property of non-equilibrium system, then ρ, p and T would be functions of time and space r and t. So we can have differential form of the above for time and space derivative. In order to fully describe a hydrodynamical system one needs to introduce average velocity $v(r,t)$, which is going to be useful in studying the dynamics of a fluid in motion. Later on we would elaborate more about $v(r,t)$. Therefore, generalizing equilibrium thermodynamic relations 2.1 to time and space coordinates, we would have:

$$\frac{\partial \rho(r,t)}{\partial t} = \rho(r,t)[\delta_T \frac{\partial p(r,t)}{\partial t} - \alpha_p \frac{\partial T(r,t)}{\partial t}] \tag{2.2}$$

Similar equation can be written for spatial derivatives instead of time derivatives:

$$\nabla \rho(r,t) = \rho(r,t)[\delta_T \nabla p(r,t) - \alpha_p \nabla T(r,t)] \tag{2.3}$$

The thermodynamic coefficients in equations 2.2 and 2.3 also are going to be spatio-temporal, but since that would lots of complexity to our equation, we assume they are constant throughout the course of action. These assumption of local equilibrium will be valid when the molecular length and time scales are small compared to the hydrodynamic length and time scales. In case of studying hydrodynamic phenomena in synaptic cleft, dimensions are small enough to make these assumptions valid.

2.3 Balance Equations

Before going further, we need to take a closer look to governing dynamics in fluid mechanics. Fluid mechanics is nothing but Newtonian mechanics added with assumption of *continuity*. This assumption states that if we have a fluid, and we grab a small portion of the fluid, the same mechanics is still going to be applied to this small part and in other words it is still fluid. But to what extent is this assumption is true, is the main topic of research and it is called *hydrodynamic limits*. Hydrodynamic limits basically is study to fill the gap between fluid mechanics and statistical mechanics, which one has deterministic nature and the other probabilistic. This bridge is basically would tell us, what is the fine line in spatio temporal scale or even considering more variables, that below that everything is probabilistic and above deterministic. Some mathematicians tried to open a field of research by proposing that laws of fluid mechanics would somehow arise from probabilistic nature of statistical mechanics and finally as a function of number of particles in system, these laws with *probability*

of one would converge to laws of hydrodynamics [30]. This discussion is out of scope of this thesis and we will continue further with fluid mechanics.

When we mix Newtonian mechanics with assumption of continuity we come up with balance equation for mass, momentum and energy. We know laws of conservation from Newtonian mechanics for mass, momentum and energy. Therefore we are going to use *flows* in context of fluid mechanics to describe these quantities. Since we have continuity assumption, we would have flow of mass, momentum and energy and we would use Newtonian mechanics to study their dynamics and how they conserve:(for the sake of simplicity dependence of functions on time and space is omitted.)

Mass Balance Equation

If we fix, a volume ΔV, according to law of mass conservation the amount of mass inside this volume must be equal to amount of mass entering this volume through surface S of this volume. Therefore if we denote density of fluid of by $\rho(r,t)$, the amount of mass inside this volume is $\int_{\Delta V} \rho(r,t)dr$, so law of mass conservation would give us:[1]

$$\frac{d}{dt}\int_{\Delta V} \rho(r,t)dr = -\int_S \rho(r,t)\cdot v(r,t)dS, \tag{2.4}$$

$v(r,t)$ here denotes bulk speed which we already defined. After applying *Stokes theorem*, to equation 2.4, which gives us relationship between divergence of a field and its flow, we would have:

$$\frac{\partial \rho(r,t)}{\partial t} = -\nabla\cdot(\rho v) \tag{2.5}$$

This is called *continuity equation*, for one component fluid. This would tell us that mass is a locally conserved field. In the case of a fluid mixtures with several components, we have to define densities for each fluid component, $\rho_k(r,t)$, which denotes the mass density of component$k$. Therefore the total density of the fluid would be sum of density of all fluid components, namely:

$$\rho(r,t) = \sum_{k=1}^{N} \rho_k(r,t) \tag{2.6}$$

Similarly, we have to define bulk fluid velocity for each fluid component, namely $v_k(r,t)$. If we had to define diffusion process in this context, it would be the movement of different fluid components relative to each other at different velocities. Similar to total mass density, the bulk velocity of fluid is going to be a function of whole fluid components and this time intuitively average velocity defines the formula, namely:

$$v(r,t) = \frac{1}{\rho(r,t)}\sum_{k=1}^{N} v_k(r,t) \tag{2.7}$$

As we have already mentioned different components move relative to whole fluid, therefore we can define a diffusion flow of one component namely $J_k(r,t)$, which is going to tell us how of much of fluid mass is carried by the bulk flow relative to whole fluid. Therefore mathematically:

$$J_k(r,t) = \rho_k(v_k - v) \tag{2.8}$$

Applying same arguments of mass conservation for case of k-component flow would give us continuity equation for k-component flow as follow:

$$\frac{\partial \rho_k}{\partial t} = -\nabla.[\rho_k v + J_k] \tag{2.9}$$

Pressure Tensor

In Newtonian mechanics, momentum of a certain mass is correlated with the forces applied to it. Before studying the momentum balance, we have to study forces applied to a small volume element, so we can import them in momentum balance. If we consider a volume ΔV, there is going to be two kinds of forces applied to it namely volume forces and surface forces. Volume forces apply to interior of ΔV, therefore the mass inside that volume which represent the points inside of it is going to take the volume forces. We can normalize the volume forces by defining a force density $f(r,t)$, which denotes the total force per unit volume. As a result of this definition, total forces applied to the volume element ΔV is the integration of force density function over this fluid element. Therefore:

$$F_{vol}(t) = \int_{\Delta V} f(r,t)dr \approx f(r,t)\Delta V \tag{2.10}$$

Before diving deep into trying to find the balance equations for momentum conservation, first we are going to take a deeper a look at concept of pressure. If we again consider a fluid element with volume ΔV, there are forces which act on the boundary or in other words on the surface of this volume element.

Mathematically speaking, a specific point at a boundary of a geometric shape is recognized by the surface vector element dS, a normal vector pointing orthogonal to surface, and therefore the effective force applied to this force element is going to be in direction of this surface element. Therefore total sum of forces applied to the surface is going to be sum of all forces at all points and we can describe this mathematically by following formula:

$$dF = -P(r,t) \cdot dS \tag{2.11}$$

where $P(r,t)$ denotes the tensor of whole forces applied to that particular surface element $dS(r,t)$ and its dot product with this surface element, implies how much if this tensor forces exerts a force in direction of that surface element. This is called the pressure tensor.

Using some mathematical tricks and *Taylor's expansion*, equation 2.11 can be simplified into for a total forces applied to a volume element ΔV:

$$\Delta F_{sur} = -(\nabla \cdot P^T(r,t))\Delta V \tag{2.12}$$

If Pressure Tensor, which of is of second-rank, only was non-zero in direction of surface element, it would have a simpler form. It would mean there are only forces in direction of surface element and there are no tangential forces to it. We get this property when fluid is at rest, or in other words $v = 0$ .Therefore in the case non-existing tangential forces the Pressure Tensor is going to be diagonal since it would be in direction of dS must be normal to the surface. Mathematically speaking it is going to be of following form:

$$P_{rest}(r,t) = p(r,t)I_{3\times 3} \tag{2.13}$$

where $I_{3\times 3}$ is the 3×3 identity matrix and the proportionality factor $p(r,t)$ is called hydrostatic pressure. From the name we can identify that, it indicates the existing forces applying to surface elements, when there is no flow. Hydrostatic pressure also can be identified beyond hydrodynamic equations and in case of a fluid in thermodynamic equilibrium it is equal to pressure defined in statistical physics framework. We can conclude that Pressure tensor has two parts, one part indicates the hydrostatic forces and the other tangential forces. Mathematically we can put it in following equation:

$$P(r,t) = p(r,t)I - \Pi(r,t) \tag{2.14}$$

I here denotes the identity matrix and $p(r,t)$ the scalar hydrostatic force predicted by thermodynamic equilibrium assumptions depending on temperature and mass density(the other thermodynamic variables). $\Pi(r,t)$ is called *deviatoric stress tensor*. The physical interpretation of equation 2.14 is that the deviatoric stress tensor are the part of the pressure tensor which identifies with tangential and shear forces and this forces case movements in fluid(static vs dynamic).

Momentum Balance Equation

According to second law of Newton, we know that, change in momentum relative to time is equal to forces applied to the system. Therefore again if we consider a volume ΔV, and we have the dynamics of forces applied to it of form equations 2.10 to 2.14 and the relations with pressure tensor, we are going to have, with using some mathematical tricks:

$$\rho(r,t)\frac{d}{dt}v(r,t) = -\nabla \cdot P(r,t) + f(r,t) \tag{2.15}$$

If we expand the pressure tensor and do some mathematical trick to total time derivative's definition we are going to have:

$$\frac{\partial \rho v}{\partial t} = -\nabla.[(pv)v - \Pi] + f - \nabla p \tag{2.16}$$

If the term $f - \nabla p$, which appears as source, is equal to zero, therefore the equation above is going to be conservatory and this makes momentum a conservative property. External forces and hydrostatic pressure acts as sources for momentum.

Energy Balance Equation

For sake of simplicity, we assume that only external forces are conservatory which means they are gradient of potential energies in the system. For the component k of the fluid this would mean that, the force F_k applied to it, comes from derivation of potential energy $\psi_k(r)$, which is function of spatial coordinates, therefore constant through time coordinate. Therefore sum of total forces would be:

$$f(r,t) = \sum_k \rho_k(r,t) F_k(r) = -\sum_k \rho_k(r,t) \nabla \psi_k(r,t) \tag{2.17}$$

Similar to bulk flow and total density we can define total potential energy for $\psi(r,t)$ for the whole fluid mixture by:

$$\psi(r,t) = \frac{1}{\rho(r,t)} \sum_k \rho_k(r,t) \psi_k(r,t) \tag{2.18}$$

If we defined energy per uni volume to be summation of potential energy $\rho\psi$ and kinetic energy $\frac{1}{2}\rho\psi^2$, therefore balance equation for total energy would be:

$$\frac{\partial}{\partial t}(\frac{1}{2}\rho v^2 + \rho\psi) = -\nabla.[(\frac{1}{2}\rho v^2 + \rho\psi)v - P.v + \sum \psi_k J_k] - P : (\nabla v) - \sum J_k. \tag{2.19}$$

F_K: $P : (\nabla v)$ indicates tensor product between total pressure tensor and gradient of velocity(intuitively this is the energy dissipated due to friction between adjacent volume elements moving along each other).

Meanwhile we can see that energy balance equation is not conservatory(In balance equations when change of one variable in on side is not equal to divergence of some quantity, which this divergence indicates the flow of quantity through surface, then that variable is not conservatory).

So have to define internal energy $u(r,t)$ which would absorb source term in energy balance equation. with certain balance equation to make total energy of system to be conservatory (divergence of a term.) We can proceed and define the total energy density in following terms:

$$\rho e = \frac{1}{2}\rho v^2 + \rho\psi + \psi u \tag{2.20}$$

where, e here is total energy density and is a function of time and space coordinates. Now we can write balance equation for internal energy. In order to do this, we have to consider that internal energy can flow throughout the fluid. The flow of internal energy is called heat flow and is denoted by Q which is also a function of time and space. The balance of internal energy is therefore related to heat flow in following way:

$$\frac{\partial}{\partial t}(\rho u) = -\nabla.[\rho u v + Q] - p\nabla.v + \Pi : (\nabla v)^{(s)} + \sum J_k.F_k, \tag{2.21}$$

$(\nabla v)^{(s)}$ is symmetric part of *gradient velocity tensor* defined by:

$$[v_{ij}]^{(s)} = \frac{1}{2}\Big\{\frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i}\Big\} \tag{2.22}$$

According to definition of this tensor, it is symmetric. The symmetric part of the Δv, shows the the deformation of the fluid element due to the bulk movement and the anti-symmetric part shows the rotation of the fluid element due to bulk flow.

Now we are have to define a framework, so we can handle introduced variables in system which we need to know their dynamics in order to fully describe our balance equations. Heat flow Q, diffusion flux J and deviatoric stress tensor Π are among these variables. The goal of non-equilibrium thermodynamics is to handle these emerged fluxes. After that we can not only describe balance equations, but also get dynamics of the property we need: Temperature.

Entropy balance

Lastly we need to balance of entropy to come up with complete set of equations. For deriving equations for entropy balance, we should use local equilibrium assumption and apply it to Gibbs-Duhem Equation for specific entropy s. We already defined s to be entropy per unit volume. So in thermodynamic equilibrium we have:

$$Tds = du - \frac{p}{\rho^2}d\rho - \sum \mu_k dc_k \tag{2.23}$$

μ_k here is specific chemical potential of component k and c_k is concentration of component k in total fluid. Later on we are going to use statistical mechanics, to derive concrete formulas for specific chemical potentials, based on variables which they depend on which would be temperature and concentration. So with local equilibrium we would have:

$$T\partial_t s = \partial_t u - \frac{p}{\rho^2}\partial_t \rho - \sum \mu_k \partial_t c_k \tag{2.24}$$

$$T\nabla s = \nabla u - \frac{p}{\rho^2}\nabla \rho - \sum \mu_k \nabla c_k \tag{2.25}$$

$$\tag{2.26}$$

Now we are going to use equations 2.24 to derive balance equation for entropy. After playing with equations and considering mass and momentum balance equations, we can derive entropy balance equation in following form:

$$\frac{\partial}{\partial t}(\rho s) = -\nabla.[(\rho s)v + \frac{1}{T}(Q - \sum \mu_k J_k)] + \sigma \tag{2.27}$$

which,

$$\sigma = -\frac{1}{T^2}Q.\nabla T + \frac{\Pi : (\nabla v)^{(s)}}{T} - \frac{1}{T}\sum J_k.[T\nabla(\frac{\mu_k}{T}) - F_k] \tag{2.28}$$

We can see that balance equation for entropy has a source term, beside a divergence term. This source term is called *entropy-generation-rate* density. *Onsager relations* in next chapter would explain the form of source function and why does it look this way. This entropy source term is not zero, due to irreversible nature of evolution of entropy.

$\Psi = T\sigma$ is defined as *dissipation function*. Dissipation function is basically sum of tensor products of some tensors of same rank and in each product there is a term which indicates the fluxes we introduced before. These are called *dissipative fluxes* which were, heat flux Q, diffusion flux J_k and deviatoric stress tensor Π. The other terms in each tensor product called the *conjugate thermodynamic force* for that flux. In thermodynamic equilibrium these dissipative fluxes do not exist and vanish. Therefore these fluxes are fundamental in non-equilibrium thermodynamics.

2.4 Onsager Relations

Now we have balance equations to describe the our system completely. But the number of equations is smaller than variables and here is the assumptions of non-equilibrium thermodynamic can add more equations to be compatible with degrees of freedom. The next assumption we need in order to study non-equilibrium systems is rooted in entropy balance equation. Intuitively speaking, vector quantities like ∇T give rise to thermodynamic forces, since they give direction to movement of particles, in our case neurotransmitters, in fluid.

Onsager or phenomenological relations which help us study these fluxes states that:
Dissipative fluxes are linear combination of thermodynamic forces. If R_α is a dissipative flux, we would have:

$$R_\alpha = \sum M_{\alpha\beta} X_\beta \tag{2.29}$$

which X_β here are thermodynamic forces. So the dissipative function would have such a form:

$$\Psi = \sum M_{\alpha\beta} X_\alpha X_\beta \tag{2.30}$$

One further result of Onsager relations is that forces and fluxes, which do not have same tensorial character, do not couple. For example deviatoric stress tensor and force resulting from temperature gradient don't couple, since first one is tensorial character 4 and second one is of 2. We will use this to simplify the processes deriving hydrodynamic equations. This is called *Marie Curie Principle*. There some other properties of these *Onsager Coefficients* $M_{\alpha\beta}$, such as symmetry, which is out of scope of this thesis and is not going to be elaborated.

The Onsager relations are called phenomenological, because first they have been observed experimentally. Though later people established theoretical explanations for them.

With the help of Onsager's reciprocal relations, we can derive complete set of hydrodynamic

equations for a binary fluid mixture, which is the basis for the thermodynamic description of the neurotransmission. Before that, we have to first derive hydrodynamic equations for case of one-component fluid.

One-Component Fluid

The dissipation function is going to take the form of:

$$\Psi = -\frac{1}{T}Q.\nabla T + \Pi : (\nabla v)^{(s)} \tag{2.31}$$

There is two dissipative fluxes in these equation, heat flux and deviatoric stress tensor and their corresponding conjugate thermodynamic forces, $-\frac{\nabla T}{T}$ and $\nabla v^{(s)}$. According to Marie-Curie Principle Q would be only linear function of just $-\frac{\nabla T}{T}$and deviatoric stress tensor only $\nabla v^{(s)}$ (due to tensorial character difference). So after some calculation and simplifying equations we would have:

$$Q = -\frac{K}{T}\nabla T \approx -\lambda \nabla T \tag{2.32}$$

this equation is called *Fourier's Law* for heat conduction. we consider T^{-1} as constant since gradient of T are not very large. So considering that, λ as a constant would be called *thermal conductivity.*

And for the deviatoric stress tensor:

$$\Pi_{ij} = \eta(\frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_j}) + (\eta_v - \frac{2}{3}\eta)\delta_{ij}\frac{\partial v_l}{\partial x_l} \tag{2.33}$$

η and η_v is respectively called shear bulk viscosity.The physical interpretation of the bulk viscosity is the amount of force needed to compress volume element. With some mathematical tricks, the Onsager coefficients now reduced to the physically more intuitive quantities, namely λ, η and η_v, since they are directly related to diffusion phenomena and therefore called transport coefficients.

Putting these results from equations 2.31 to 2.33 into mass and momentum balance equations 2.5, 2.9 and 2.16 would give us famous *Navier-Stokes* equation:

$$\rho[\frac{\partial v}{\partial t} + (v.\nabla v)v] = -\nabla p + \eta\nabla^2 v + (\frac{1}{3}\eta + \eta_v)\nabla(\nabla.v) + f \tag{2.34}$$

Solving these equation along with other balance equations would give us bulk velocity profile of the fluid. Unfortunately this equation is highly non-linear and hard to simulate numerically. On the other hand, since we assume that we are going to have bulk flow in system, we would not need to solve this equation.

Next step would be to derive equations for heat and entropy balance. Combining mass balance and entropy balance equation 2.27 we would have:

$$\rho T(\frac{\partial s}{\partial t} + v.\nabla s) = -\nabla.Q + \Pi : (\nabla v)^{(s)} \tag{2.35}$$

After applying local equilibrium assumption to thermodynamic relationship of:

$$Tds = c_p dT + \frac{T}{\rho^2}(\frac{\partial \rho}{\partial T})_p dp \tag{2.36}$$

which c_p is specific heat capacity of the fluid. Combining this with entropy balance equation we have. Now we can derive total heat equation:

$$\frac{\partial T}{\partial t} + v.\nabla T = a_T \nabla^2 T + \frac{\alpha_p T}{\rho c_p}[\frac{\partial p}{\partial t} + v.\nabla p] \tag{2.37}$$

$a_T = \frac{\lambda}{\rho c_P}$ is thermal diffusivity. In the introduction of thesis we talked about Penne's bio-heat equation, which is nothing but simplified version of total heat equation.

The balance laws comprised with heat and Navier-Stokes equation gives us the complete set of equations we need to describe the hydrodynamics for an one-component fluid. It is worth mentioning that the hydrodynamic equations can also be derived from statistical mechanics starting from the Liouville and Boltzmann equation [23], which is out of scope of this thesis. With these results at hand we can do more calculations and derive the hydrodynamic equations for binary mixture case:

2.5 Hydrodynamic Equations For Binary Mixture Fluid

The dissipative function 2.28 is going to have more terms:

$$\Psi = -\frac{1}{T}Q.\nabla T + \Pi : (\nabla v)^{(s)} - J.[T\nabla(\frac{\mu}{T})] \tag{2.38}$$

J here refers to diffusion of one component (in our case it is going to be the neurotransmitter) relative to whole solution. $\mu = \mu_1 - \mu_2$: difference in chemical potential of two components.

In order to expand this equation, we need to remember that, how chemical potential was a function of concentration and pressure and expand its gradient relative to temperature. So we would have:

$$\nabla_T \mu = (\frac{\partial \mu}{\partial c})_{T,p} \nabla c + (\frac{\partial \mu}{\partial p})_{T,c} \nabla p, \tag{2.39}$$

and

$$\frac{\partial \mu}{\partial t} = (\frac{\partial \mu}{\partial c})_{T,p}\frac{\partial c}{\partial t} + (\frac{\partial \mu}{\partial p})_{T,c}\frac{\partial p}{\partial t} \tag{2.40}$$

which c here is the concentration of first component or the component which we are considering its diffusion in solution. In our case it would be concentration of neurotransmitter.

Now, we have to consider Onsager relations 2.29 and 2.30 for heat and diffusion flux in system to derive hydrodynamic equations. The calculations for Onsager matrix here is omitted. By using local equilibrium assumptions, simplified version of Onsager relations are going look like this at the end:

$$Q = -\lambda \nabla T + [\mu - T(\frac{\partial \mu}{\partial T}) + k_T(\frac{\partial \mu}{\partial c})_{p,T}]J \tag{2.41}$$

$$J = -\rho D \nabla c + \frac{k_T}{T}\nabla T + \frac{k_p}{p}\nabla p, \tag{2.42}$$

λ is thermal conductivity and D is diffusion coefficient of first component in another, k_T is dimensionless thermal diffusion ratio and k_p baro-diffusion coefficient. Depending on problem k_T can be considered as a constant to simplify equations (especially in liquid-liquid mixtures). We are going to ignore the effect of baro-diffusion, since we assume the effect of pressure gradients on heat propagation in our case of study is infinitesimal. Baro-diffusion is mainly important in problems of geophysics, or the centrifuges where the gradients of pressure is large.

We can now proceed with deriving with complete set of hydrodynamic equations for a binary mixture by forming the related Onsager relations. Nothing changes for the deviatoric stress tensor, therefore we still have Navier Stokes equatioahlengthn valid for the bulk flow and total fluid mixture density.

If we turn continuity equations into a continuity equation 2.5 for concentration, it would take this form:

$$\rho(\frac{\partial c}{\partial t} + v.\nabla c) = -\nabla.J \tag{2.43}$$

which $c = \frac{\rho_1}{\rho}$. Taking Onsager relations into account we would derive balance equation for concentration:

$$\frac{\partial c}{\partial t} + v.\nabla c = D\nabla^2 c + \frac{k_T}{T}\nabla^2 T \tag{2.44}$$

which is total *diffusion equation* considering *Soret effect*, diffusion of concentration due to temperature gradient and neglecting baro-diffusion, diffusion due to pressure gradient. $v.\nabla c$ is the *advection term*, which diffusion of concentration along bulk flow and since we assumed that we have no bulk flow this term would also be omitted.

Now for deriving balance equations for temperature we need to use local equilibrium equations for generalizing Gibbs-Durhem equations 2.23 and 2.24 which we already did in previous chapters and by inserting and combining them with Onsager relations and equation for dissipative function and entropy balance 2.27 and 2.28, we would get:

$$\rho T\frac{ds}{dt} = \lambda\nabla^2 T + \rho D[k_T(\frac{\partial\mu}{\partial c})_{p,T} - T(\frac{\partial\mu}{\partial T})_{p,c}][\nabla^2 c + \frac{k_T}{T}\nabla^2 T] \tag{2.45}$$

Simplifying this according to equations 2.36 and 2.40, would give us balance equation for heat and omitting terms, which are square of a gradients plus the term related to pressure (as we assumed constant pressure throughout our modelling) we get:

$$\frac{\partial T}{\partial t} + v.\nabla T - \frac{k_T}{c_p}\frac{\partial\mu}{\partial c}\frac{\partial c}{\partial t} = a_T\nabla^2 T \tag{2.46}$$

This is total heat equation, which the term $\frac{k_T}{c_p}\frac{\partial\mu}{\partial c}\frac{\partial c}{\partial t}$, demonstrates heat propagation due to concentration gradient, is called *Dufour Effect*. In other words, heat is carried, with a complex dynamic, by neurotransmitter molecules.

We also assume that there is no bulk flow during release and there is not convection, so v can be considered zero and we don't have to solve Navier-Stokes equation for velocity. Therefore we neglect velocity from equations. So what we had for a heat equation in case of one-component fluid, is the same dynamics with exception that here, concentration flow, is also contributing to diffusion of heat.

From a thermodynamic perspective, we have what we need to describe fully the binary mixture of two fluid or in our case neurotransmission. But there is also one dynamic that we should cover before having a complete set of equations describing the whole process and that is how existence of electrical field in synaptic cleft can affect concentration profile of charged neurotransmitters, in our case glutamate.

2.6 Thermodynamical Fluctuations and Noise: Prospective Research

In the section of understanding temperature, we discussed the fundamental definition of temperature from statistical physics point of view. We defined the concept of ensemble and how we can calculate macroscopic thermodynamic quantities by averaging over ensemble. From probabilistic perspective, ensembles resemble probability density functions over particles' coordinates in phase space and we denoted these ensemble functions by $f(x,t)$ which showed invariant properties with respect to time and space.

In order to calculate a certain thermodynamic variable A, we defined a observable $a(x)$ with respect to probability density function and took an average. Therefore, $A = E_f(a)$, which is a expectation relative to probability distribution and this tells us we are dealing

with an uncertain quantity which shows variance. We can calculate variance of this random variable as follows:

$$\Delta A = E_f(a^2) - E_f(a)^2 \tag{2.47}$$

Therefore by calculating this variance, we can basically get some idea about *fluctuation* of that variable from expected value. In thermodynamic equilibrium , for example the fluctuation of temperature from baseline value would be [5]:

$$< \Delta T >^2 = \frac{k_B T^2}{C_V} \tag{2.48}$$

which here C_V refers to heat capacity at constant volume. As we can see thermal fluctuations can be source of noise in the system. They are relatively straightforward to calculate in case on static fluid in thermodynamic equilibrium, but for fluid in motion and in case of non-equilibrium thermodynamic, situation gets pretty complex. Since fluid is in motion and non-equilibrium thermodynamic, therefore the ensemble might be invariant under Hamiltonian, so through we have consider evolution of ensemble function through time trajectory as well and spatial averages are not enough. Therefore time correlation in the fluctuations of thermodynamic quantities might be an issue. In our case, we have dissipative processes in the system such as viscosity, thermal conduction and we have so far seen how they are correlated with so called thermodynamic forces. In order to form a framework for dealing with fluctuations in such systems, rather than starting from microscopic statistical physics ensemble, one can inject uncertainty into these system from a macroscopic perspective.

As we have seen, we have formed hydrodynamic equations of motion for fluids. These equations gave us dynamics of temperature, concentration, bulk velocity and so on, through time and space. In order to compute fluctuations for these quantities, we can add appropriate additional terms to equations so they could capture uncertainty in given time and space coordinate [2].

In section for Onsager relations, we have seen that how dissipative fluxes relate linearly to thermodynamic forces. But in presence of fluctuations these linear relationships might not be exact and appropriate noise term can be added to Onsager relations. As an example we can consider, Fourier law for heat flux, where heat flux was a linear function of gradient of temperature. In case of fluctuation added, is going to be in following form:

$$Q = -\nabla T + \delta q \tag{2.49}$$

where δq indicates the noise or fluctuation, which gives uncertainty to Fourier law. δq is basically a random variable and depending on context can follow certain probability distribution.

Taking these additional terms into account, the balance laws which we derived in previous sections are going to turn to set of stochastic partial differential equations (SPDE)

and these describe evolution of thermodynamic fields and densities under influence of fluctuating dissipative fluxes. Dealing with SPDEs requires complex mathematical framework and techniques, but in context of fluid dynamics there are techniques invented to apply in order so solve simplified versions of fluctuating balance equations. For example, famous *Fokker-Planck* equation describes the form of diffusion equation considering stochastic thermal noise. However doing similar for our coupled electro-diffusion of mass-heat transfer is more challenging and providing solutions for that even more. Considering solving equations, we formed for evolution of temperature with existing noise, might give us a more comprehensive treatment of dynamics of temperature and this might be a possible future research topic.

2.7 Electrical Field in Non-Equilibrium Thermodynamics

We can now continue our attempt to add electrical field to our equations rising from non-equilibrium thermodynamics. As we have seen by now, in the works of Rusakov et al, there exists an electrical field in synaptic cleft affecting the motion of neurotransmitters. So how we add the term of electrical field n diffusion equation for concentration? From Onsager relations 2.29 we already know that the diffusion flux of neurotransmitter is going to be in this form:

$$J = -\rho D \nabla c + \frac{k_T}{T} \nabla T \tag{2.50}$$

However, from electromagnetic theory, we know that charged particles have a flux in direction of electrical field and the force applied to it, is going to be proportional to amount of charge in unit concentration. In other words:

$$J_{electrical} \propto c \tag{2.51}$$

$$J_{electrical} \propto \nabla \phi \tag{2.52}$$

which ϕ here is the electrical potential and its gradient would be electrical field generated in synaptic cleft due to charged neurotransmitters and molecules.

One can easily obtain the coefficient for relation between diffusion flux and concentration. After putting that into total diffusion flux our final form of diffusion flux would be:

$$J = -\rho D \nabla c + \frac{k_T}{T} \nabla T + \frac{ze}{k_B T} \nabla \phi \tag{2.53}$$

Another way of reaching equation above would be forming total electrochemical potential equation. The electrochemical potential of a solution is going to be form of [8]:

$$\mu = RT \log c + zF\phi \tag{2.54}$$

which ϕ is the electrical potential. Therefore this argument can be used that, in solutions, the diffusion flux is going to be in direction of gradient of electrochemical potential or in

other words concentration moves in a direction, which has lower electrochemical potential. Considering the gradient of electrochemical potential, we would have the extra term related to electrical field in our diffusion equation. Combining this with what we had for diffusion flux in non-equilibrium case, with extra term of Soret effect, we would have total diffusion flux as written above.

Chapter 3

Summary and Parameters of The Model

In the introduction of thesis we talked about how studies before used Penne's bio-heat equation in order to describe diffusion of heat in a biological system and by solving this equation numerically or analytically one would get temperature map for that system(in spatial and time coordinates). We also said that origin of this equation comes back to fundamental heat equation, which we derived a complete form of it in the section of non-equilibrium thermodynamics. We also mentioned that how studies before treated neurotransmission as a diffusion process and we also derived a complete form of it as well. Fortunately, the equations of heat and concentration can describe many processes down to mesoscopic scale which would include our system of study as well, whether it is neurotransmission or regulation of heat through blood flow.

Overall in order to simply explain the model, we can say that beside total heat and concentration diffusion in simplest form, we have three extra dynamics going on here: first *Soret Effect* which was diffusion concentration due to temperature gradient in system or basically particles diffusing in direction of temperature gradient. We would later see that numerically this term is negligible. Second, energy or heat is diffused also due to concentration gradient or in other words heat moving in direction of gradient of concentration. This phenomenon is called *Dufour Effect* and a bit more complicated than just what we have mentioned, since it also describes the generation of heat due to chemical potential mixture of two fluids. Third is the diffusion of neurotransmitter concentration due to existence of of electrical field called *Electro-diffusion*.

Multi-Physics Model of Neurotransmission

After considering all the existing dynamics in our systems which their summary described by equations 2.44, 2.46 and 2.53 from previous sections, the final set of equations for diffusion of neurotransmitter concentration and heat would be in this order:

$$\frac{\partial c}{\partial t} = \nabla \cdot (D\nabla c + D\frac{ze}{k_B T}c(\nabla \phi)) + D\frac{k_T}{T}\nabla^2 T + F_1 \tag{3.1}$$

$$\frac{\partial T}{\partial t} - \frac{k_T}{c_p}\frac{\partial \mu}{\partial c}\frac{\partial c}{\partial t} = \chi \nabla^2 T + F_2 \tag{3.2}$$

$$\nabla^2 \phi = \frac{F}{\epsilon} z.c \tag{3.3}$$

Here, c is the the concentration of neurotransmitter, T temperature field in synaptic cleft. ϕ is the electrical potential generated by charged particles in the system by neurotransmitters and as we already said, this electrical potential should match pre- and post-synaptic membrane potentials when we look at its value at boundaries. This is treated as boundary condition for electrical potential and we would talk about it more in section for simulation parameters.

We are going to choose glutamate as the neurotransmitter in our equation and using its properties such as its diffusion coefficient and so on. The reason for this choice is that:

- Glutamate is the most prevalent neurotransmitter in brain and in nearly 80 percent of cases it is the main neurotransmitter in excitatory synapses.

- Diffusion of glutamate is studied more frequently compared to other neurotransmitters and therefore its fluid mechanical properties is more measured and available in literature.

- As we mentioned before, since glutamate is one of major neurotransmitter in excitatory synapses, and we are trying to study electro-diffusion effect in excitatory synapses, it makes a good choice to narrow down our study to glutamate. Also since it is negatively charged, electrical field can influence its movement. In general, especially when it comes to nature of heat propagation and temperature dynamics, we would see that related individual properties of a neurotransmitter such as diffusion coefficient and thermal diffusivity are going to play a small role in making useful hypotheses regarding temperature profile of neurotransmission. Therefore, we don't lose much generality by narrowing down our choice.

D is diffusion coefficient of neurotransmitter, here glutamate and according to previous studies we can safely assume it is around $10^{-10}\frac{m^2}{s}$(though in literature its value described

to be around 0.4 $\mu m^2/s$ and it has been measured in *Artificial cerebrospinal fluid*, it's not going make big difference in simulations. Overall different experiments show some degree variability in measured diffusion coefficient of glutamate not only due to difference in content of solvent they have used, also due to the different geometries and bounding area they use for experiment which affects the coefficient value.) [4]. z is electrical valance of neurotransmitter and for glutamate is -1 [8], and e is unit electrical charge.

k_T is dimensionless thermal diffusion ratio and overall the term $D\frac{k_T}{T}\nabla^2 T$ indicates Soret effect and it is included in diffusion equation for concentration. Throughout the whole process, k_T is not constant, but for the sake of simplicity we consider as a constant value. In liquid-liquid mixtures k_T is around $10^{-3} - 10^{-2}$ [3] and we put it approximately 10^{-2} for our simulation.(Fortunately numerical simulations give us robust results relative to change in thermal diffusion ratio).

We have to calculate $\frac{\partial \mu}{\partial c}$ in terms of local temperature and concentration. We assume this mixture is an ideal solution. Simplifying this it would mean that chemical potential of mixture would be the linear combination of the two components. More precisely, $\mu = \mu_1 - \mu_2$, which μ is the chemical potential of the mixture and μ_1 and μ_2 are the chemical potentials of the solvent and solute respectively normalized per mole. Therefore using some statistical mechanical techniques calculating chemical potential mixture of the whole solution as a function of temperature and concentration, we would have [5]:

$$\mu = \frac{T \log c + const}{m_1} - \frac{\mu_0 - Tc}{m_2} \tag{3.4}$$

k_B is Boltzmann constant and it appears in the term and μ_0 constant chemical potential. Therefore we would have:$\frac{\partial \mu}{\partial c} = N k_B T'.(\frac{1}{c.m_1} + \frac{1}{m2})$. The term$-\frac{k_T}{c_p}\frac{\partial \mu}{\partial c}\frac{\partial c}{\partial t}$ refers to Dufour effect, which one can see its related to rate change of concentration. Here m_1 is glutamate molar mass ($\approx 147\frac{g}{mol}$), [32] m_2 water molar mass ($\approx 18\frac{g}{mol}$), [33] N Avogado's number and T' is assumed to be constant temperature which indicates to temperature of as solution in steady equilibrium state and we use this as an approximation to handle the nonlinearity of the equations when we simulate them.. For more details one can refer to Landau's *Statistical Physics* [5]. Its value should be around initial values, so for our simulations we put it around ($\approx 310K$). Simulation results are pretty robust to this value, since Dufour effect is very small. In Dufour effect term, c_p refers to water's specific heat capacity $\approx 4.10^3 \frac{J}{Kg.K}$. Generally due to lack of data, we assume that extracellular space is mainly water, so that's why we are dealing with water's characteristics here.

χ is thermal diffusivity of glutamate. χ indicates how fast heat propagates through a volume of material. Since, there is not data available for thermal diffusivity of glutamate, we are going to assume that is going to have smaller value than thermal diffusivity of water (this is due to the fact that glutamate have higher density than water and density appears in denominator of thermal diffusivity). At given temperatures, thermal diffusivity of water is $\approx 2.10^{-7}\frac{m^2}{s}$ [34]. Therefore we're going to run several simulations for different values of χ to observe the behaviour of solution relative to this value.

ϵ is electrical permittivity of solution. F Faraday Constant $\approx 96485 \frac{C}{mol}$. The Poisson equation basically relates to well-know Poisson equation for charge and electrical potential to concentration of neurotransmitter. Since it is the neurotransmitter which carries the charge.

F_1 Source function for concentration and F_2 Source function for temperature. We mainly use these two functions for release of neurotransmitters from vesicle, leak or clearance and re-uptake of neurotransmitters in cleft.

Solving these equations above analytically is a hard problem to tackle, since it is a coupled system of non-linear partial differential equations. But fortunately there are methods to approximate solutions numerically. *Finite Element Analysis* is the method that we are going to use for solving these equations numerically. In next section, we will give a brief introduction to finite element methods.

Chapter 4

Introduction to Finite Element Analysis

Partial differential equations are usually defined on a domain, in which we are trying to solve them. This domain is usually a subset of *Euclidean Space* or more generally a *Manifold*. In our case, it is going to 2-dimensional euclidean plane. The domain can take a complex shape, but usually it is approximated by a *Polygon*, like the Figure 2. This would make *Triangulation*, a concept we will later define.

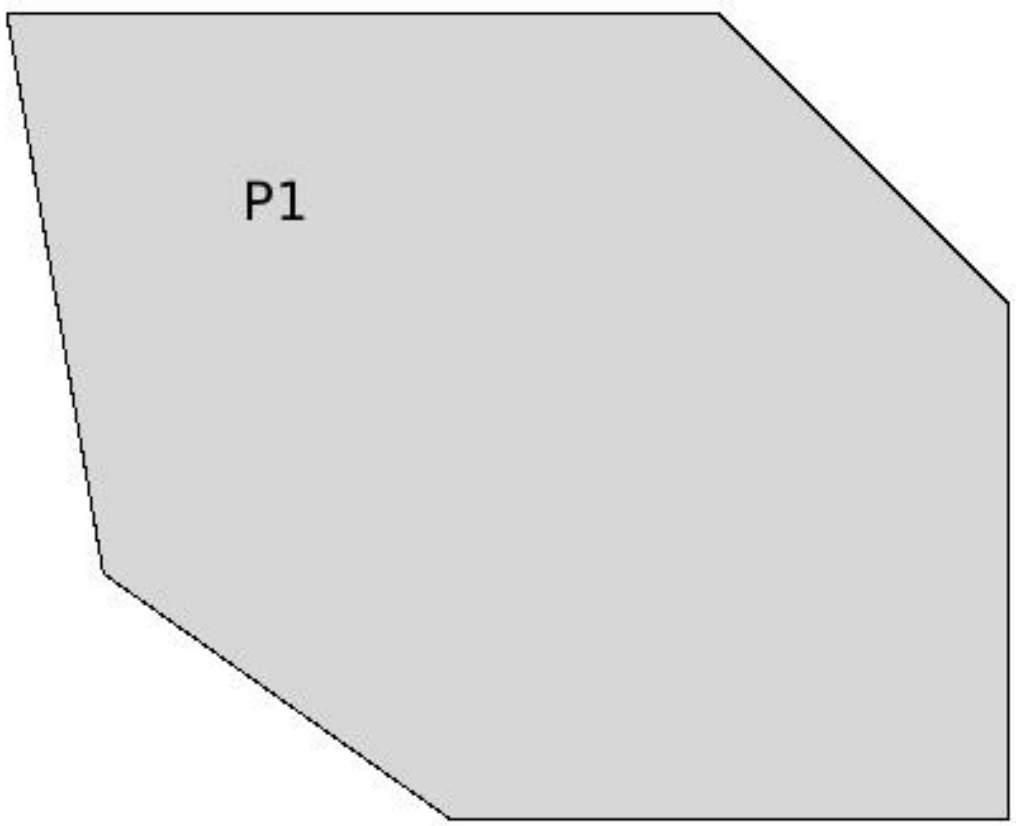

Figure 2: A typical Polygon as geometry usually has been used, but in advanced platform and techniques the geometry can be much complex.

Partial differential equations, usually require more information rather than just their basic form, to be solvable. Depending on the problem, it could be *initial condition* (for PDE's which have time as a variable). But mostly we need to define *Boundary Condition* for our equations. Boundary conditions determine, how solutions to our equations should behave in boundary of geometry, in which they are defined. When we have, *Dirichlet Boundary Condition*, would tell us what values our solution would take on the boundary. An example of a real physical problem would be temperature distribution. If we have a differential equation, describing dynamics and distribution of temperature inside a system, such as heat equation and if I connected boundary of my system or geometry with a heat source, whose temperature is controllable, by another device or third party object, there in boundary we always have a temperature, well defined and any solution might conform to this value at boundary. When we have *Von Neumann Boundary Condition*, it defines how is flow of solution through the boundary, or mathematically behaviour solution's first derivative. An example of a real physical problem would be, if have system of particles and particles distribute according

to certain dynamics, such as diffusion equation and particles could move freely through the boundary, therefore Von Neumann boundary condition would tells us the amount of particles flow through the boundary. There some other forms of boundary condition, but these two are the main ones we are going to use in our problems [28].

Now, we are going to use simple example of a differential equation so we can proceed with the introduction of finite element methods. Consider *reaction-diffusion* equation below:

$$-\Delta u + cu = f, x \in \Omega \tag{4.1}$$
$$u = g_0, x \in \Gamma_D \tag{4.2}$$
$$\partial_n u = g_1, x \in \Gamma_N \tag{4.3}$$

u here is a scalar function defined on domain Ω and the last two equations describe Dirichlet and Von Neumann boundary condition respectively. This form of differential equation, consisting of derivatives, called *Strong Form*. But in order to use Finite Element Analysis we should write our differential equation in a weak form. Before that we need some tools and one of those is *Green Theorem*.

Green Theorem is nothing, but generalization of integration by parts to higher dimensions and specific geometries. It states that if we have another function v defined on our domain Ω, we would have:

$$\int_\Omega (\Delta u)v + \int_\Omega \nabla u \cdot \nabla v = \int_\Gamma (\partial_n u)v \tag{4.4}$$

Left hand side of integration is taken on main domain and right hand side on the boundary of the domain. Using green theorem for our u in the reaction-diffusion equation 4.1, we would have:

$$\int_\Omega (\Delta u)v + \int_\Omega \nabla u \cdot \nabla v = \int_\Gamma (\partial_n u)v = \int_{\Gamma_D} (\partial_n u)v + \int_{\Gamma_N} (\partial_n u)v \tag{4.5}$$

Therefore using reaction diffusion terms in our green equation we would have:

$$c\int_\Omega uv + \int_\Omega \nabla u \cdot \nabla v = \int_\Gamma fv + \int_{\Gamma_N} g_1 + \int_{\Gamma_D} (\partial_n u)v \tag{4.6}$$

We can put $v = 0$ on Γ_D, so the term for Dirichlet boundary on equation 4.6 will be abolished. Therefore *Weak Formulation* would be defined like below:

Find u such that:

$$u = g_0, \; on \; \Gamma_D \tag{4.7}$$
$$c\int_\Omega uv + \int_\Omega \nabla u \cdot \nabla v = \int_\Gamma fv + \int_{\Gamma_N} g_1, \; for \; every \; function \; v \; such \; v = 0 \; on \; \Gamma_D \tag{4.8}$$

In context of finite element analysis, v is called test function and such functions basically form a basis for the space of functions which u lies in, and by weak formulation calculations, we are going to find out what is going to be weight of every v for our function u.

We are going to limit the search space for functions u, so the solutions can have properties which can avoid the complexities later on. We are going to search in *Sobolev Space* for such a function defined by:

$$H(\Omega) = \left\{ u \in L^2(\Omega) | \frac{\partial u}{\partial x_1}, \frac{\partial u}{\partial x_2} \in L^2(\Omega) \right\} \tag{4.9}$$

This means that integration of both the function u and its first derivatives are limited on space Ω. We are not going to dig further in definition of this space. Depending on our problem, we can again limit the search space. For example for our test function v in weak formulation we can consider a subspace of this Sobolev space, which its elements have become null on Dirichlet boundaries.

In order to proceed further with Finite Element Analysis, we have to review another main core concept of these methods namely discretization. Discretization here, could refer to discretization of the domain or geometry we are working with or the space of functions, Sobolev space we already defined or weak formulation of the differential equation. This discretization would help us to tackle solving equations numerically.

4.1 Finite Element Spaces

First, we would go further to define certain space of linear functions namely polynomials of degree one defined in following way:

$$p(x_1, x_2) = a_0 + a_1 x_1 + a_2 x_2 \tag{4.10}$$

The set of these functions is denoted by P_1. In order to uniquely determine a polynomial of degree N, we need certain number of linear equations for its coefficients, which would mean knowing its value on some number of points, and for linear polynomials in euclidean plane this number is 3, which means knowing its value on vertices of a triangle (It's equivalent to solving a linear system having number of equations equal to variables). As we can see, we can form all function inP_1 by linear combinations of 1, x_1 and x_2, which makes this spaces a vector space of dimension three . The three values of the function on the vertices of a triangle which uniquely defines it, will be called the *local degrees of freedom*. We will see later how the space of polynomial functions would be a basis in order to search for solutions.

In next step we have to find ways to descretize our space or geometry. *Triangulation* is one way. Triangulation is the method of of partitioning a domain or geometry, into triangles which cover all the domain and intersect only in edges or nodes, but their *interior* do not

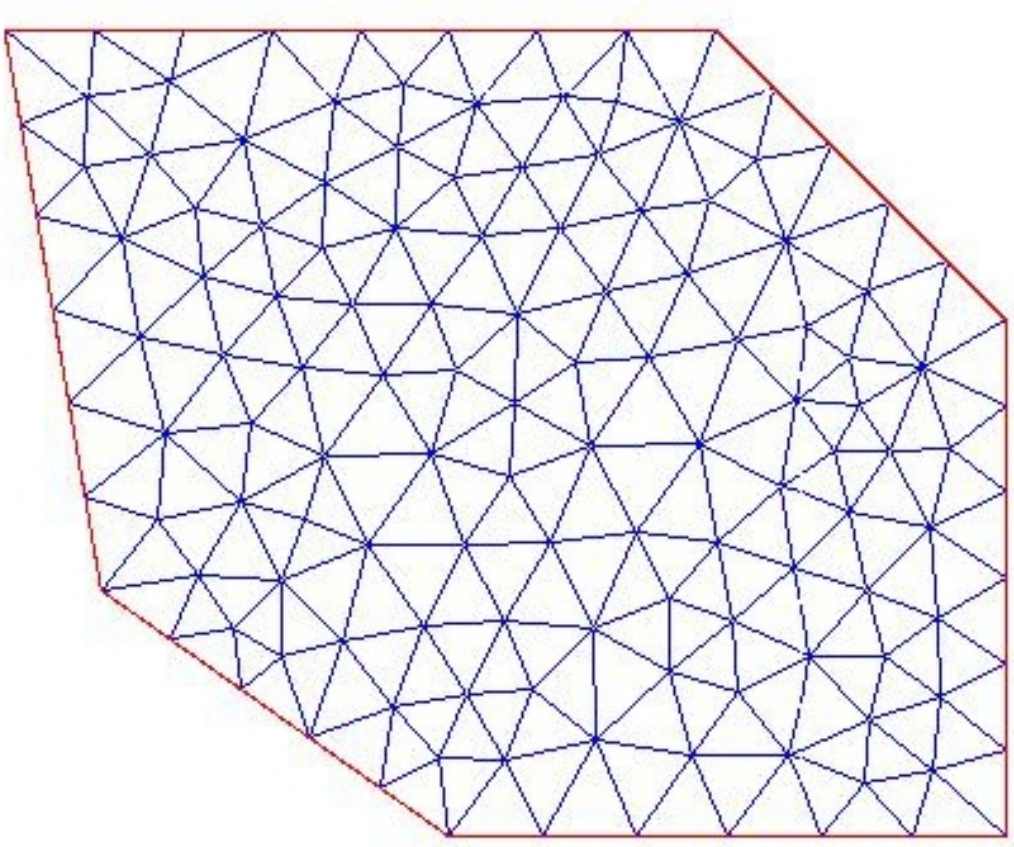

Figure 3: Triangulation Example.

overlap. Also nodes should never lie on the edge of another triangle, in other words node for one triangle should be one for another. See Figure 3 below for an example.

We now consider the space of **Piece-wise Linear Functions** defined by a specific triangulation Θ_h. Consider a function whose restriction to a triangle K of this triangulation would be linear. We already mentioned a linear function is unique by such a definition and since triangles share vertices, this function would be continuous. The space of such functions is:

$$V_h = \left\{ u_h \middle| u_h|_K \in P_1, \forall K \in \Theta_h \right\} \tag{4.11}$$

V_h is called P_1 finite element space. Supposedly we have N vertices on triangulation. For every node on this triangulation, we can define a indicator polynomial,$\phi_i \in V_h$ which is only non-zero on that node. This function is going to be unique and defined in following way:

$$\phi_i(P_j) = \begin{cases} 1 & i = j \\ 0 & i \neq j \end{cases} \tag{4.12}$$

These functions form a basis for V_h and we can write simply every other function $u_h \in V_h$ in following way:

$$u_h = \sum_{j=1}^{N} u_h(P_j)\phi_j \tag{4.13}$$

Therefore $\dim V_h = N =$ number of vertices. So far we have taken functions inside the domain into account. Now we have to proceed how to put boundary conditions into our framework. We first need some terminology. A Dirichlet edge, contains a boundary condition that deals with value of solution (fixed values independent of differential equation), therefore it belongs to Γ_D. A*Neumann edge* is an edge of a triangle, which flow of the solution on this boundary is specified, therefore it belongs to Γ_N. The vertices of the Dirichlet edges are called *Dirichlet nodes*. Values on Dirichlet nodes are important, since when we attempted to use test functions in weak formulation, we restricted them so that they vanish on Dirichlet boundaries. Therefore our set functions which we want to deal with in our triangulation we want them to vanish on Dirichlet nodes to makes things easier. Beside we want them to be part of Sobolev space of domain. Call this subset $V_h^{\Gamma_D}$. We can construct this concretely by requiring the coefficients of $u_h(P_j)$ to be zero when P_j is part of Dirichlet nodes. Finally we can form our initial problem to be able to express it in numerical approximations:

Find $u_h \in V_h$ such that:

$$u_h(P_j) = g_0(P_j), \forall j \in \ Dirichlet\ Nodes \tag{4.14}$$

$$c\int_\Omega u_h\phi_i + \int_\Omega \nabla u_h \cdot \nabla \phi_i = \int_\Gamma f\phi_i + \int_{\Gamma_N} g_1\phi_i, \forall i \in \ Non - Dirichlet\ Nodes \tag{4.15}$$

If we write down u_h in terms of basis functions ϕ_i, it is going to have the following form:

$$u_h = \sum_{i \in Non-Dirichlet} u_i\phi_i + \sum_{j \in Dirichlet-Nodes} g_0(P_j)\phi_j \tag{4.16}$$

If we apply this to weak formulation, it's going to have following form:

$$\sum_{j \in Non-Dirichlet} \Big(\int_\Omega \nabla\phi_j \cdot \nabla\phi_i + c\phi_i\phi_j \Big) u_j$$

$$= \int_\Omega f\phi_i + \int_{\Gamma_N} g_1\phi_i - \sum_{j \in Dirichlet-Nodes} \Big(\int_\Omega \nabla\phi_j \cdot \nabla\phi_i + c\phi_i\phi_j \Big) g_0(P_j)$$

So we reached from original differential equation in strong form we had, to system of linear equations for coefficients u_j. So in simplest form, when we have triangulation and its basis functions, our task would be form such a linear system to derive coefficients for basis functions so we can have our solution.

$W_{ij} = \int_\Omega \nabla\phi_j \cdot \nabla\phi_i$ is called **stiffness matrix** and $M_{ij} = \int_\Omega \phi_i\phi_j$, **mass matrix**. The stiffness matrix has this property if, if the nodes i and j are not adjacent, or in other words they don't belong to same triangle then $W_{ij} = 0$. We have similar results for M_{ij}, which makes stiffness and mass matrix to be greatly sparse or in other words to have lots of zeros in their array elements. Computers have methods of saving spars matrices in a compact form, so that they will take less memory and be time-wise efficient regarding computations. We can efficiently compute integrals and put them in way to be computationally efficient and this is called *assembly methods.*

First consider what we have so far: a Triangulation, a finite element space, stiffness and mass matrix accordingly. Integrals taken over Ω are basically sum of integrals over the different triangles. So for stiffness matrix we would have:

$$w_{ij} = \int_\Omega \nabla\phi_j \cdot \nabla\phi_i = \sum_K \int_K \nabla\phi_j \cdot \nabla\phi_i = \sum_K w_{ij}^K \tag{4.17}$$

On each triangle we are going to define three local nodal basis functions. First assign a number to each of the three vertices of a triangle K:

$$p_1^K, p_2^K, p_3^K \tag{4.18}$$

Then consider the functions $N_1^K, N_2^K, N_3^K \in P_1$ such that $N_\alpha^K(p_\beta^K) = \delta_{\alpha\beta}$. These are basically basis functions for nodes that belong to triangles. Therefore we can extract stiffness weight from these functions and use them accordingly. We would have:

$$k_{\alpha\beta}^K = \int_K \nabla N_\alpha^K \cdot \nabla N_\beta^K = w_{n_\alpha n_\beta}^K \tag{4.19}$$

All other elements of the matrix W^K are zero. Therefore stiffness matrix would be sum of these matrices:

$$W = \sum_K W^K \tag{4.20}$$

This is basically assembly, computing weights from each triangle and putting them in one matrix. We can do something similar for mass matrix.

Now in order to make concrete computations, we need more framework. The main idea is that since every object in triangulation is a triangle and we are defining functions on a particular triangle in $2-D$ space, we can define a triangle called *reference element* and do computations on this triangle. Since every two triangle is transformable to each other by linear transformation, we can have functions defined on one-triangle, hopefully transfer to others by similar transformation, so that they wouldn't loose properties. We define our

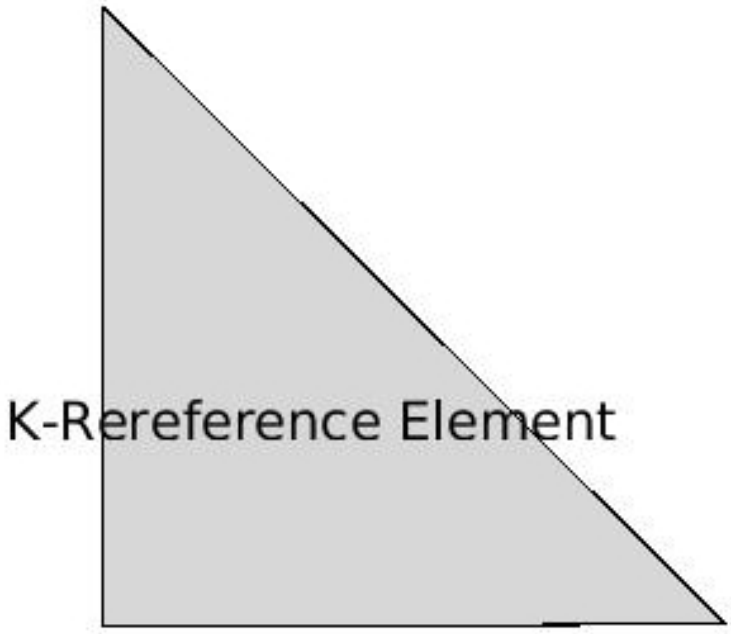

Figure 4: The Reference Element.

reference element to be a triangle of following Figure 4

For triangles, the reference element is the triangle with vertices:

$$\tilde{p_1} = (0,0), \tilde{p_2} = (1,0), \tilde{p_3} = (0,1) \tag{4.21}$$

We denote (ξ, η) the coordinates in the reference element and (x, y) in the physical element. Going from one to other triangle, we would need an affine transformation or in other words a linear transformation plus some bias vector. We denote this by F_K for the bijective transformation from reference element to triangle K and its linear part, which would be a 2×2 matrix, by B_K. Now we can form basis functions on triangle K based on basis functions for reference element. Suppose $\tilde{N}_1$, $\tilde{N}_2$, $\tilde{N}_3$ are the basis functions for reference element and similarly N_1, N_2, N_3 basis functions for triangle K. Since the transformation is bijective and each nodes corresponds to one node in other triangle, we would have:

$$N_\alpha^K(x,y) = \tilde{N}_\alpha(F_K^{-1}(x,y)) \tag{4.22}$$

This is how basis functions correspond to each other. Therefore similarly using chain rules and *Jacobian* of the transformation, which is B_K, we can correspond gradients to each other as well, in following way:

$$\nabla N_\alpha^K = (B_K^T)^{-1}((\tilde{\nabla}\tilde{N}_\alpha) \circ F_K^{-1}) \tag{4.23}$$

$(B_K^T)^{-1}$ is the inverse of the transpose of the matrix B_K. From this formula we can go further and form stiffness and mass matrix of triangle K from reference element. The change of variables applied to the integral of the local mass matrix gives:

$$\int_K N_\alpha^K N_\beta^K = |detB_K| \int_{\tilde{K}} \tilde{N}_\alpha \tilde{N}_\beta \tag{4.24}$$

Something more complex we would have for stiffness matrix:

$$\int_K \nabla N_\alpha^K \cdot \nabla N_\beta^K = |detB_K| \int_{\tilde{K}} ((\tilde{\nabla}\tilde{N}_\alpha) \circ F_K^{-1}) \cdot ((\tilde{\nabla}\tilde{N}_\beta) \circ F_K^{-1}) = |detB_K| \int_{\tilde{K}} C_K \tilde{\nabla}\tilde{N}_\alpha \tilde{\nabla}\tilde{N}_\beta \tag{4.25}$$

which $C_K = B_K^{-1} B_K^{-T}$.

Depending on partial differential equation, we are dealing with or the source functions in the strong form, boundary conditions and so on, we can have similar transformations, from reference element to current triangle we are doing computations on. Here we just presented stiffness and mass matrix computations, since they play a fundamental role in finite element analysis.

The P_1 finite element method for the reaction–diffusion problem with homogeneous Dirichet conditions is therefore an example of **Galerkin method**. What we did so far, we created a

space of functions and by limiting ourselves to a subspace of this function space we wanted to search for functions that satisfy *weak formulation* which we already had, for every test function v. Finally this turned into a problem of solving a linear system, since we could write down every function in that subspace as a linear combination of basis elements of that space and the coefficients of this combination satisfied a linear equations which was rising from our original differential equation. Our algorithms of search for this function would satisfy *Cea's Lemma*, which states[28]:

$$\|u - u_h\| \leq \frac{M}{\alpha} inf\Big\{ \|u - v_h\| \Big| v_h \in V_h \Big\} \tag{4.26}$$

which V_h states the search space for approximate solutions, and M and α are constants depending on problem, and u_h is the approximate solution.

This error bound for P_1 finite element method is of the following form:

$$\|u - u_h\| \leq Ch\Big(\int_\Omega |\partial_{xx} u|^2 + |\partial_{yy} u|^2 + |\partial_{xy} u|^2 \Big)^{\frac{1}{2}} \tag{4.27}$$

The constant C depending on the coefficients of the problem, on the geometry of the physical setting and h is the size of the longest edge of the triangulation. The error bound requires the second derivatives of the solution to be square–integrable, which is not always the case. Also note that if u is a polynomial of degree one, this error bound is zero and u_h is exactly u. Since the bound is proportional to h, therefore method a *method of order one.* This means that if you make the longest edge half its size, you should only expect the error to be divided by two.

The low order, makes P_1 not very appealing to for solving numerical PDEs. Using higher order methods would tackle this problem. We can form linear function spaces of P_2, P_3 and so on based on degree of the polynomials we are going to use at its elements. Therefore for P_2, it is going to be the space of polynomials of degree of maximum 2. Therefore:

$$P_2 = \Big\{ a_0 + a_1 x + a_2 y + a_3 x^2 + a_4 y^2 + a_5 xy | a_0, ..., a_5 \in \mathbb{R} \Big\} \tag{4.28}$$

Since dimension of P_2 is 6, we would need 6 points on a triangle to fully determine a polynomial by those values. Therefore, Let us take a triangle K and let us mark six points as nodes: the three vertices of the triangle plus, the **midpoints** of the three edges. We can go on similarly, define basis functions, reference element, stiffness and mass matrices and so on for the triangulation relative to P_2. The error rate for P_2 would be in following form:

$$\|u - u_h\| \leq Ch^2 \|u\|_{3,\Omega} \tag{4.29}$$

the new Sobolev *semi-norm*, $\|u\|_{3,\Omega}$ uses the third order partial derivatives of u. The result is valid only when this last semi-norm is finite, which is much more to require than what we had at the beginning. Accordingly to form of error it is going to be of order two, which

is good news, since leads to more precision to the formed solution, by using just smaller triangles. We can go one and continue examples for higher order elements and for example in P_3 case, the error rate would be in order of three.

4.2 Time-Dependant Problems

The methods we have introduced so far, they are designed in order to solve PDEs which are only spatial dependant. The problems, which their solution evolves with time is not covered entirely by this method. The set of equations we have derived for thermo-diffusion in previous section, are time dependant, therefore we need methods in order to tackle this.

As we have seen numerical methods in finite element analysis, the core idea is to be able to discretize everything including spatial coordinate, the domain and geometry, function spaces and so on. In time-dependant problems we also have to categorize methods based on how they discretize problems, with taking heat equation as an example in mind:

- Methods that first discretize in time coordinates and then solve the equation in space coordinates. Supposedly problem is defined on time interval $[0, t]$ and we discretize this interval into small steps $t_1 < t_2 < t_3 < ... < t_n = t$ and we supposes solution is steady during a step and we discretize time partial derivatives accordingly. So time derivative for $\frac{\partial u}{\partial t}$ is going to discretized into:

$$\frac{\partial u}{\partial t} = \frac{u_n - u_{n-1}}{\tau} \tag{4.30}$$

  here u_n denotes solution at time t_n and τ is the time interval between different nodes in discretization, assuming we divided interval into equal steps. Using discretized form of partial derivative to time, the discretized heat equation is going to be of following form:

$$\frac{u_n - u_{n-1}}{\tau} = \Delta u_n \tag{4.31}$$

  accordingly by knowing the solution at time = 0, u_0, we can recursively form solutions at later times and at every time step, we have to use finite element method to find a solution.

- methods that discretize in space coordinates and solve equations in time coordinates. If descretize space and then try to solve the problem in time coordinate, what we will have is basically a system of Ordinary Differential Equation(ODE). This method is called *Method of Lines*.

It has some advantage and disadvantages, depending on the problem, to use specific method. For example, in some problems, it's common to use an adaptive triangulation, which gets finer in next steps of problem and this can improve accuracy of approximate solution, but then methods of line is not applicable, since it requires a fixed triangulation. MATLAB PDE Toolbox uses the method of discretizing in time coordinates first.

Chapter 5

Numerical Simulation

5.1 Simulation Setup

We are using **MATLAB**, specifically *PDE toolbox*, to simulate our coupled system of PDEs 3.1. This toolbox uses Finite Element Methods to solve partial differential equations.

First, we create a geometry as it represents the processes going on in synaptic cleft, see Figure 5. We have two release sites (from neurophysiology we know that there is always limited number of sites of release, which vesicles bind to and release their neurotransmitters) and they are depicted as small rectangles, which binded to synaptic cleft) and the height of cleft is very narrow and looking from a $2-D$ perspective and making it simplified looks like a rectangle. We simplify the geometry of the simulation, rather than having a single vesicle binding and releasing their material, their accumulative release their content from vesicle sites. We reduce random binding on membrane (as we cannot have a dynamic moving geometry when simulating PDEs) to two constant big sites, releasing their content through time. Therefore vesicle fusion is neglected.

Source function for both temperature and concentration considered to be a step function with a constant duration of 4 μs and this number reflects on time duration of membrane fusion. We can write down source function for temperature as $f = \Delta T_0 \sum_n \iota_{[n,n+\Delta t]}$, which ΔT_0 indicates temperature difference between vesicle material and synaptic cleft, ι the identity function, n the time of release and Δt as duration of the release. We just chose a random number for Δt, due to lack of data on this duration time and the fact that we are dealing with several bindings simplified as one. For other parameters of source function, we experiment with different values and results will be summarized in our heuristic equation 5.2. Also the simulation results don't show any pattern with varying this duration time number. Therefore it's not simple to specify about nature of this parameter and we just treat it as constant during simulations. However for several different values of these parameter that we ran simulations, when treated as constant, the pattern of final steady temperature dependence is going to be valid for all numbers. We could incorporate more complicated source functions like trignometric or exponential functions and that could be more realistic. But unfortunately simulations did not converge in that case due to highly non-linear nature of equations.

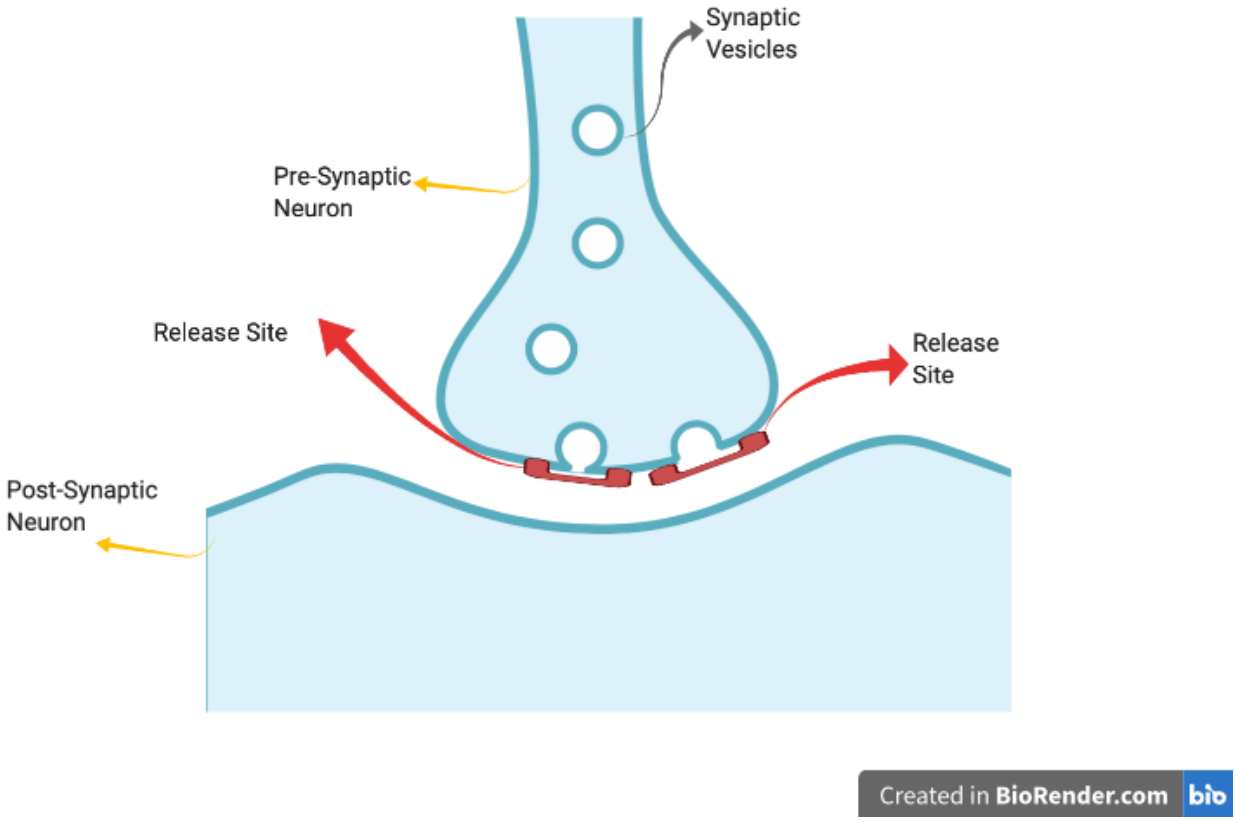

Figure 5: A schematic drawing of neurotransmission, which indicates existence of 2-3 release site.

Then we have to non-dimensionalize our system of PDE 3.1 to be compatible with the geometry. Suppose that x and t are non-dimensionalized spatial and time coordinates and x_0 and t_0 are the conversion factors. Most suitable conversation factor would be:

$$\frac{Dt_0}{x_0^2} = 1 \tag{5.1}$$

We consider the characteristic length of to be the approximate height of synaptic cleft, which is around 20 nm. In our geometry 20 nm is going to be equal to non-dimensionalized scale of 0.1. With these two numbers assumed, and if we use the relation between conversion factors and diffusion coefficient then 1 non-dimensionalized second is going to be equal to 40 μs.

Temperature and concentration in our equations need initial conditions. We put baseline initial condition for both synaptic cleft and release sites at 310 Kelvin. We just assumed this random number close to body temperature, however we are going to study temperature fluctuations relative to baseline. Therefore for any initial value, fluctuations can be shifted and there is no harm in this assumption. For concentration, we assume concentration at release sites is 0.99 and at synaptic cleft is 0.01 (we put a non-zero value to avoid singularities in our equations).

Both our three scalars, temperature, concentration and electrical potential need boundary conditions. For temperature and concentration we put a very weak Von-Neumann boundary condition. For electrical potential, we need to go back to neurophysiology. First thing we have to mention is that we have neglected the fundamental phenomenon of collision between molecules (for more details please refer to introduction of the thesis). Therefore the interface between two mixture is non-existent.

For boundary conditions of electrical field we have to differentiate between two cases of *Metabotropic* and *Ionotropic Receptors*. In latter, the receptors of neurotransmitters are located on ion channels and therefore binding neurotransmitters on them would lead ion channels to open immediately and flow of ions through channels would change the electrical potential of post-synaptic membrane. Therefore the effect on neurotransmitters on changing post-synaptic membrane potential is immediate and there is not much delay between activation of pre-synaptic and post-synaptic neuron, which is the case in our simulations. Therefore the functions we used in order to represent boundary conditions for electrical potential, i.e the pre- and post-synaptic membrane potential are look-alike sinusoidal functions, which their peak have nearly 200-500 microseconds delay from each other. So the electrical field effect has its course due to difference between these two potentials. Figure 6 shows the membrane potential for pre- and post-synaptic neuron in case Iontropic receptor [7]:

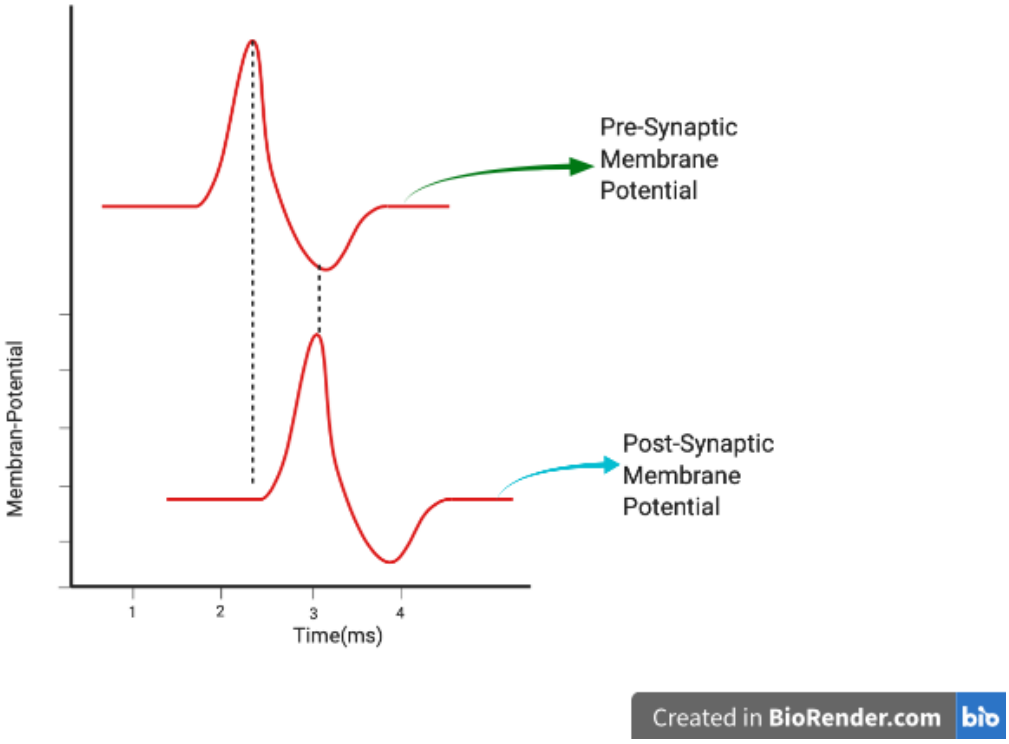

Figure 6: Pre and Post-synaptic memebrane potential for Ionotropic receptor

Therefore in order to have a simplified approximation of boundary conditions of electrical field, we are going to use Trignometric functions to describe the boundary conditions. For pre-synaptic we use $3 \times 10^{-2} - (8 \times 10^{-2}) * sin(\frac{t}{25}) * (\frac{\pi}{2}))$ and for post-synaptic, $-5 \times 10^{-2} + (8 \times 10^{-2}) * sin(\frac{t}{25}) * (\frac{\pi}{2}))$. Number 25 in these two functions refer to non-dimensionalized total time of simulation, which in reality would be equivalent to $1ms$, approximate time of action potential propagation [7].

MATLAB, uses square triangulation for the geometry and for mesh size, we use 0.025(synaptic cleft height is 0.1 for example) and as we already mentioned simulation time is 25 in non-dimensionalized setting, which is equal to $1ms$. We use 2000 time step to run simulations.

5.2 Simulation Results

Temperature Distribution

As we have already mentioned, thermal diffusivity of glutamate is unknown and therefore we are going to experiment with different values of χ to observe the behaviour of solution. If we assume thermal diffusivity of solution is smaller than thermal diffusivity of water, therefore in non-dimensionalized scale, the upper bound for the thermal diffusivity is going to be $\approx 2 \times 10^3$. Second assumption is that thermal diffusivity must be bigger than diffusion coefficient of glutamate, which is case the for must of solutions, due to fast diffusion heat compared to matter. Therefore, we experiment χ for values between 2 (2 times bigger than diffusion coefficient non-dimensionalized) and 2000.

The result is as following; for every value of χ, there is a specific a time point t_0, which after that temperature distribution throughout the geometry is going to be uniform. The bigger the χ the smaller t_0 is going to be, since heat would diffuse faster throughout geometry. For the range of values we are experimenting with, t_0 is going to be relatively small compared to 1 mili-second and it is going to be in range of nano-seconds, to microsecond. Therefore for this part of simulation, we temporarily change the setting and we simulate the PDEs in $1\mu s$ equivalent of 0.025 in non-dimensionalized scale, with same amount of steps (2000). We find t_0 by method of finding a time-step in which variance of temperature matrix goes below 0.0001. The result of simulation and different values of χ is plotted in Figure 7. We can see the inverse relationship between χ and t_0.

Before reaching a point, that temperature will be uniformly distributed in every time step, it has a non-uniform distribution, and this non-uniformity will depend also on Von-Neumann boundary condition for temperature. If Von-Neumann Condition is stronger then temperature would reach boundaries faster than inner areas. Figure 8 shows such a case for the evolution of temperature in every 150 nano-seconds (every 300 steps in simulation), for the case of $\chi = 2 \times 10^{-8}$, (20 non-dimensionalized).

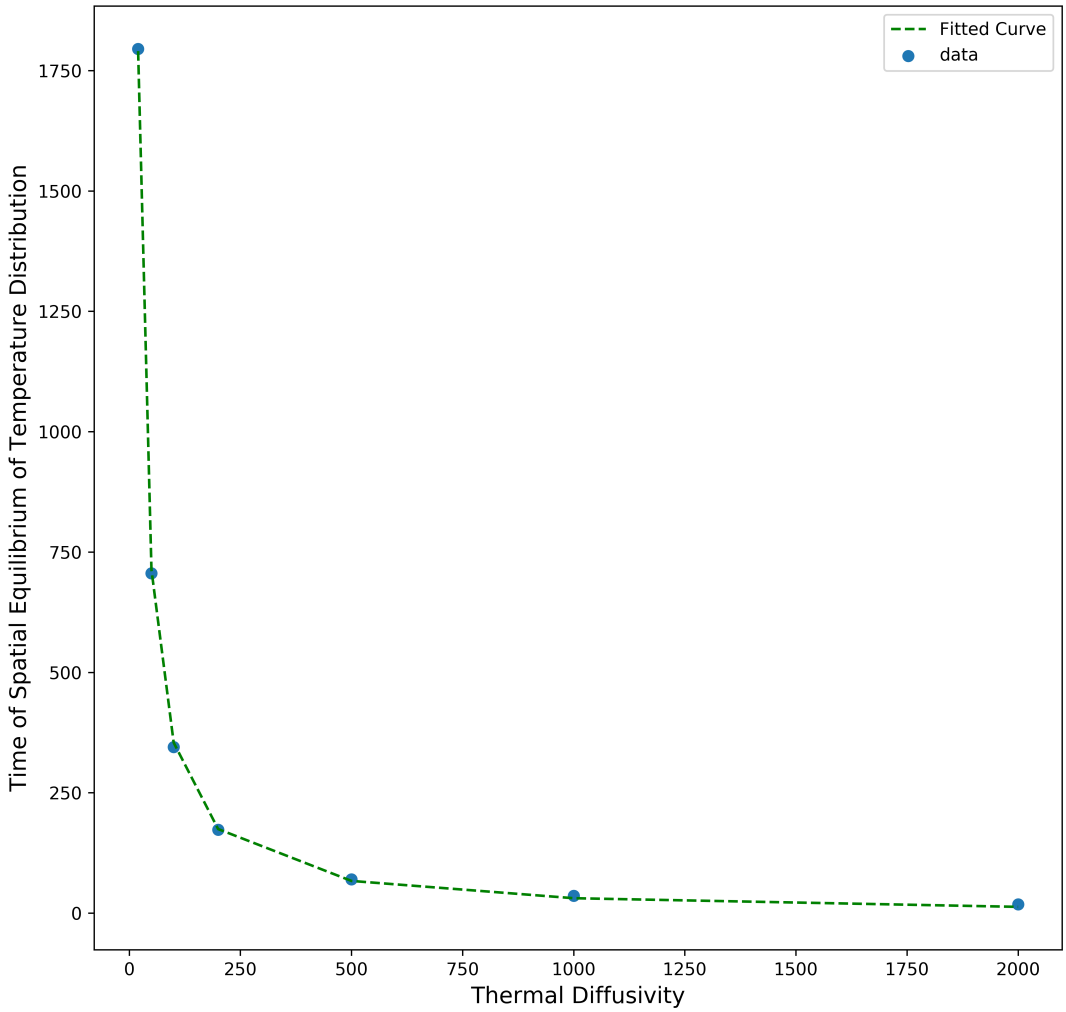

Figure 7: The time-step when the simulations of temperature reaches spatial equilibrium thereafter plotted against thermal diffusivity χ. Since all-simulations are run in 2000 time-steps and total time of $1\mu s$, we use number of the step for the benchmark of reaching such a equilibrium. X-axis shows thermal diffusivity non-dimensionalized, for real value should be multiplied by $10^{-10}\frac{m^2}{s}$.

Overall the explanations for our observations is that the temperature sources for heat diffusion come from two parts: first the source and boundary condition and secondly **Dufour Effect**. So the dynamic can be explained in following manner: in first time step of simulation the heat diffusion equation tries to reach balance caused by source and Dufour effect, then

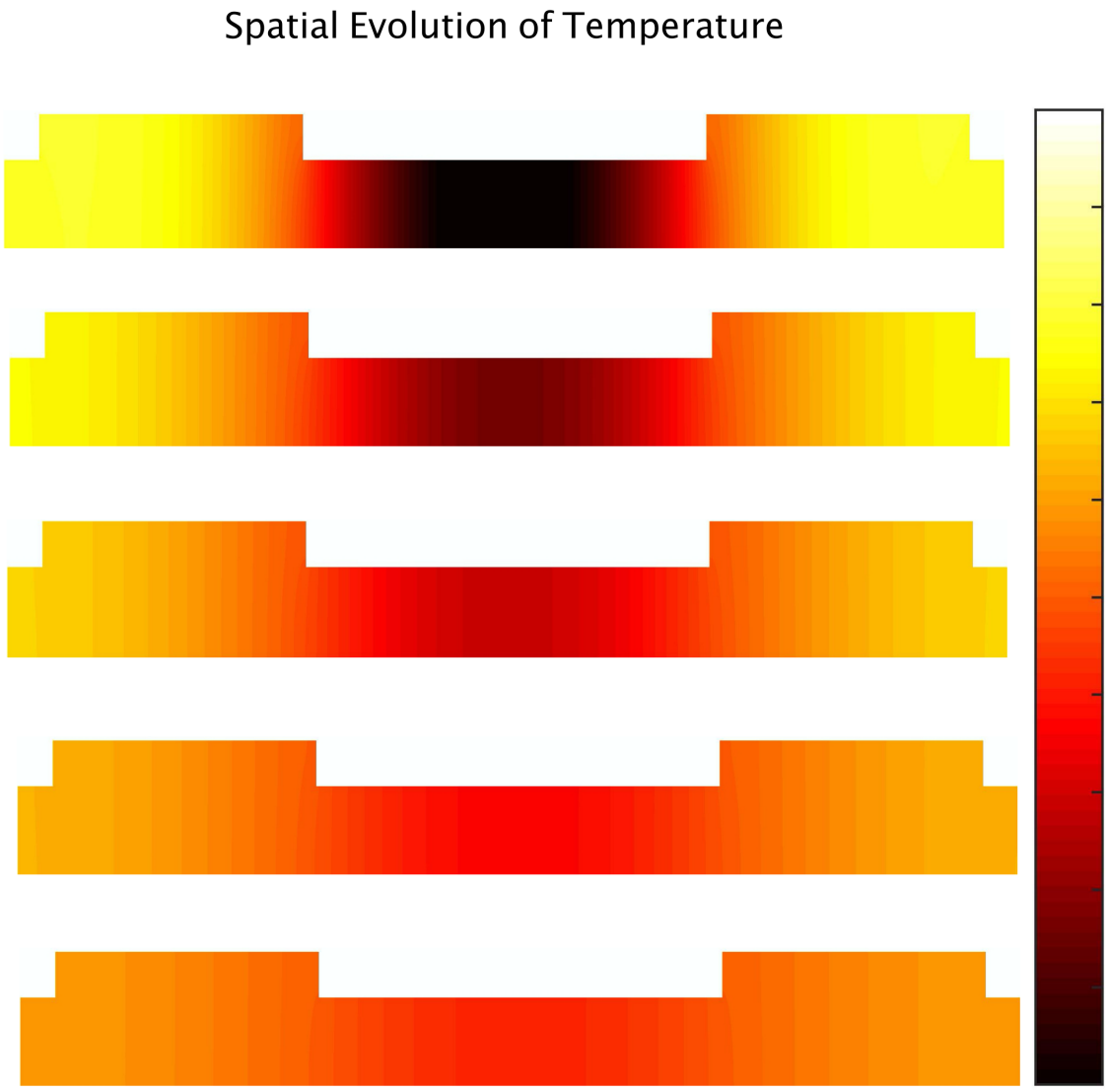

Figure 8: Time evolution of temperature for a specific χ. As we can see through time, temperature becomes spatially homogeneous. The color-bar refers to min value of 310.06 Kelvin and maximum values of 310.3 Kelvin.

it reaches equilibrium. In next time step, there is no initial imbalance, just Dufour effect and heat diffusion tries to reach equilibrium caused by this and this continues. And this dynamic of reaching equilibrium is pretty fast due to big thermal diffusion coefficient.

According to simulations, the steady state temperature, when run simulations in larger time-scale (original 1 ms) is almost invariant under using different values of χ. As a result we fixate on a specific value of χ, in our case equal to water's (2×10^3, non-dimensionalized) to study steady state temperature. We know that after a time t_0 the temperature in every step of simulation is going to be uniform throughout geometry. Therefore we can use **mean spatial temperature** to study its evolution. After running simulations for different cases and playing with parameters for the source, boundary conditions, number of release, and so on, one can determine that there are several factors that temperature in final step depends on:

- Number of release
- Magnitude of source function for temperature, which indicates temperature difference between vesicle material and intracleftic volume.
- Geometry and form of source function
- Total Dufour Effect

Number of release

Investigating case by case respectively, first we begin by number of release. If we have a source function for temperature as we have defined it as $f = \Delta T_0 \sum_{n=1}^{N} \iota_{[n,n+\Delta t]}$, with constant ΔT_0, every time we have a release there is going to be heat pumping into system with a constant duration. Our simulation results shows the more release we have, more increase in final step temperature we are going to observe and this has a linear correlation with number of release N . Number of release here treated as number of jumps in source step function as we already explained. Figure 9 shows the final temperature versus number of release plotted against each other:

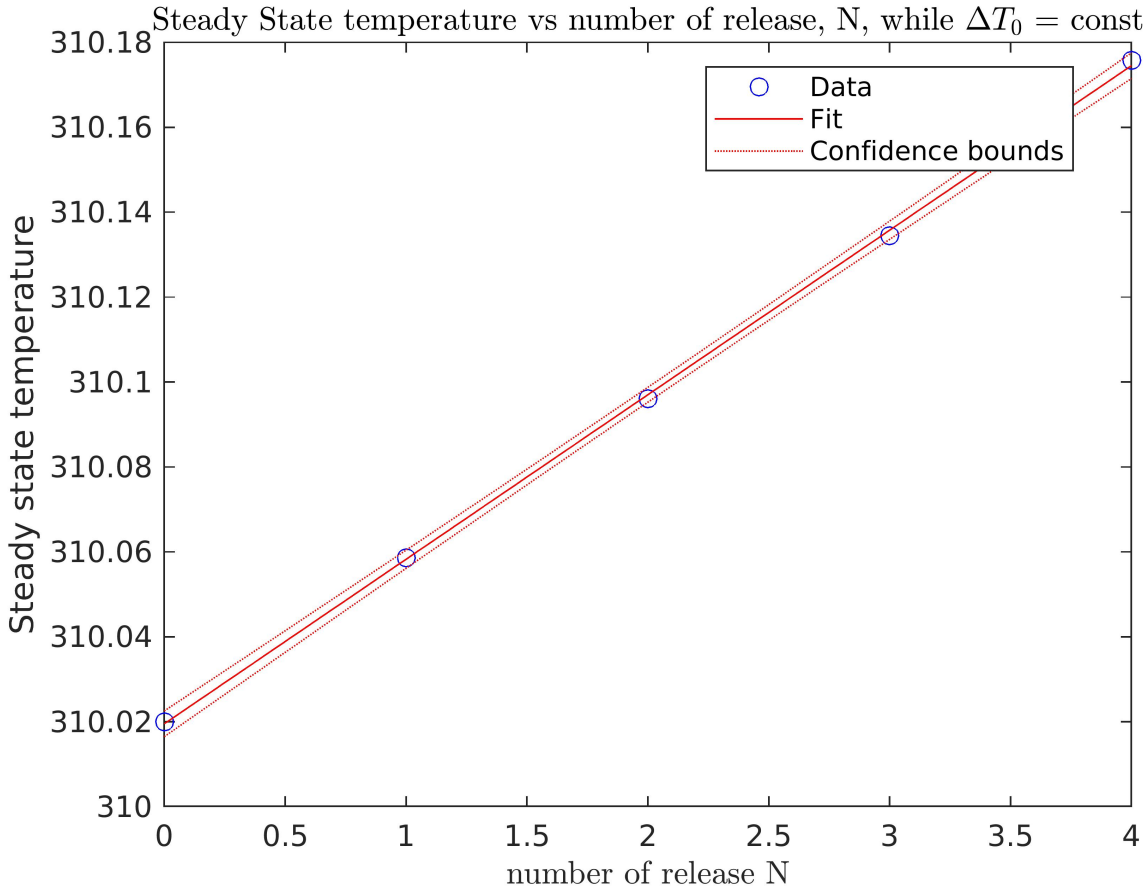

Figure 9: Steady State Temperature vs Number of Release

We have fitted a linear regression model for steady state temperature vs number of release and Figure 10 is the glossary of the coefficients, R-squared and so on:

Estimated Coefficients:

	Estimate	SE	tStat	pValue
(Intercept)	310.02	0.00095061	3.2613e+05	6.3579e-17
x1	0.038743	0.00038809	99.832	2.2157e-06

Number of observations: 5, Error degrees of freedom: 3
Root Mean Squared Error: 0.00123
R-squared: 1, Adjusted R-Squared: 1
F-statistic vs. constant model: 9.97e+03, p-value = 2.22e-06

Figure 10: Fitted Linear Regression Steady State Temperature vs Number of Release

Initial condition or source: ΔT_0
As we already said this indicates the temperature difference between neurotransmitters coming from intracellular or release site and synaptic cleft. By treating other variables such as number of release N as constant we can see pattern below if increase this temperature for discrete values such as 1,2,3,... Kelvin:

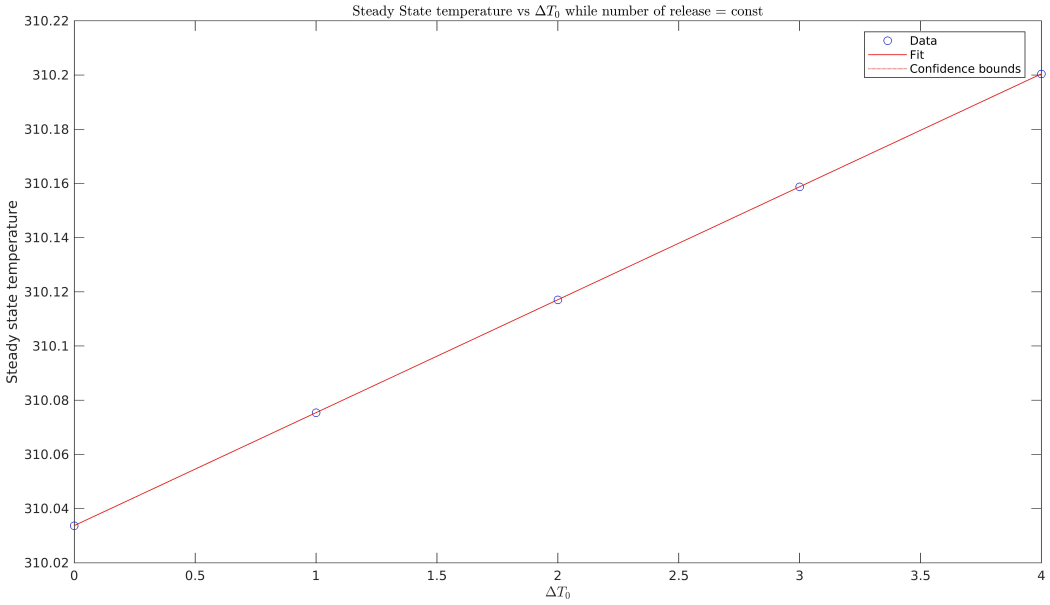

Figure 11: Steady State Temperature vs initial source temperature ΔT_0

We also fitted a linear regression to Steady State Temperature vs initial source temper-

ature ΔT_0 and below we can observe related numbers we are expecting:

Estimated Coefficients:

	Estimate	SE	tStat	pValue
(Intercept)	310.03	6.8239e-06	4.5433e+07	2.3515e-23
x1	0.041684	2.7859e-06	14963	6.5834e-13

Number of observations: 5, Error degrees of freedom: 3
Root Mean Squared Error: 8.81e-06
R-squared: 1, Adjusted R-Squared: 1
F-statistic vs. constant model: 2.24e+08, p-value = 6.58e-13

Figure 12: Fitted Linear Regression to Steady State Temperature vs initial source temperature ΔT_0

Geometry and Source function
The effect of geometry, source function duration and simulation setup is on the coefficients of the linear regression. For our geometry if look at linear regression results, we can see for every Kelvin for temperature difference between cleft and neurotransmitters there is going to be 0.1 Kelvin increase in steady state temperature. If we had for example one release site instead of two this would be smaller. The other aspects of geometry such as, boundary shapes, height of cleft and ratio between height of cleft and width of cleft this is going to be affected.

Dufour Effect
If we take a closer look at both linear regression results we can see there is a bias value(x-intercept) of approximately 0.03 Kelvin. This means if we had no release of temperature difference between cleft and neurotransmitters were zero, this would be the increase in steady state temperature. This value comes from Dufour effect which introduced in heat diffusion equation. If we run a heat diffusion equation without this term, therefore there would be zero increase in final steady state temperature. This Dufour Effect also states how much heat released from mixing synaptic vesicles inner material and extracellular matrix in synaptic cleft, due to increase in entropy and change in chemical potential mixture of the system and for our system this is 0.03 Kelvin or 30 mili-Kelvin.

Formulation of The Results for Steady State Temperature

So far we have seen what factors final temperature depends on and we fitted linear regression, just for sake assurance and scientific rigour and we observed there was perfect linear

correlation between final temperature and those variables stated below:

Heuristic Model of Temperature Change

- Number of release: N
- Difference between synaptic vesicles temperature and synaptic cleft extracellular matrix :ΔT_0
- Geometry: α the constant coefficient dependant on Geometry and form of source function
- Total Dufour Effect: δ

Accordingly we came up with following heuristic formula to describe steady state temperature increase relative to baseline:

$$\Delta T = \alpha N \Delta T_0 + \delta \tag{5.2}$$

For $N\alpha\Delta T_0 > Const$ simulations did not converge and scope of our heuristic formula is therefore is limited to simulations we ran. Another thing we can comment on is that number of release in source function was treated as having several jumps in a step function. With same number of jumps or another words number of release, we experimented with random time gaps between these jumps. The final temperature was only the function of the number of jumps and didn't show any dependency on this randomness. There is also possibility of non-constant ΔT_0 at every release, which could be either variable randomly or dependent on previous state of temperature profile of synaptic cleft. We address this issue in discussion chapter.

Contribution of Degredation to Temperature Distribution

We have already found out what affects final temperature in steady state. Another study we did was to take a look at evolution of temperature, while Dufour effect present, and see what happens if neglect some terms from equations. So in our cases there was electrical field effect, reuptake or degradation. Re-uptake is presented as source in equations not in direct forms. We estimated certain percentage of concentration is re-uptaken or degraded and we included this in source term as $-\beta c$ which β is a constant represents fraction of concentration is taken away, a value between 0.1 and 0.7.

With running several simulations, we found out that neglecting fields doesn't affect constant temperature increase during simulation except for reuptake. If we remove reuptake source from equations, therefore the final state temperature is going to be same as initial

increased temperature due to initial release. We can see graphically from Figure 13:

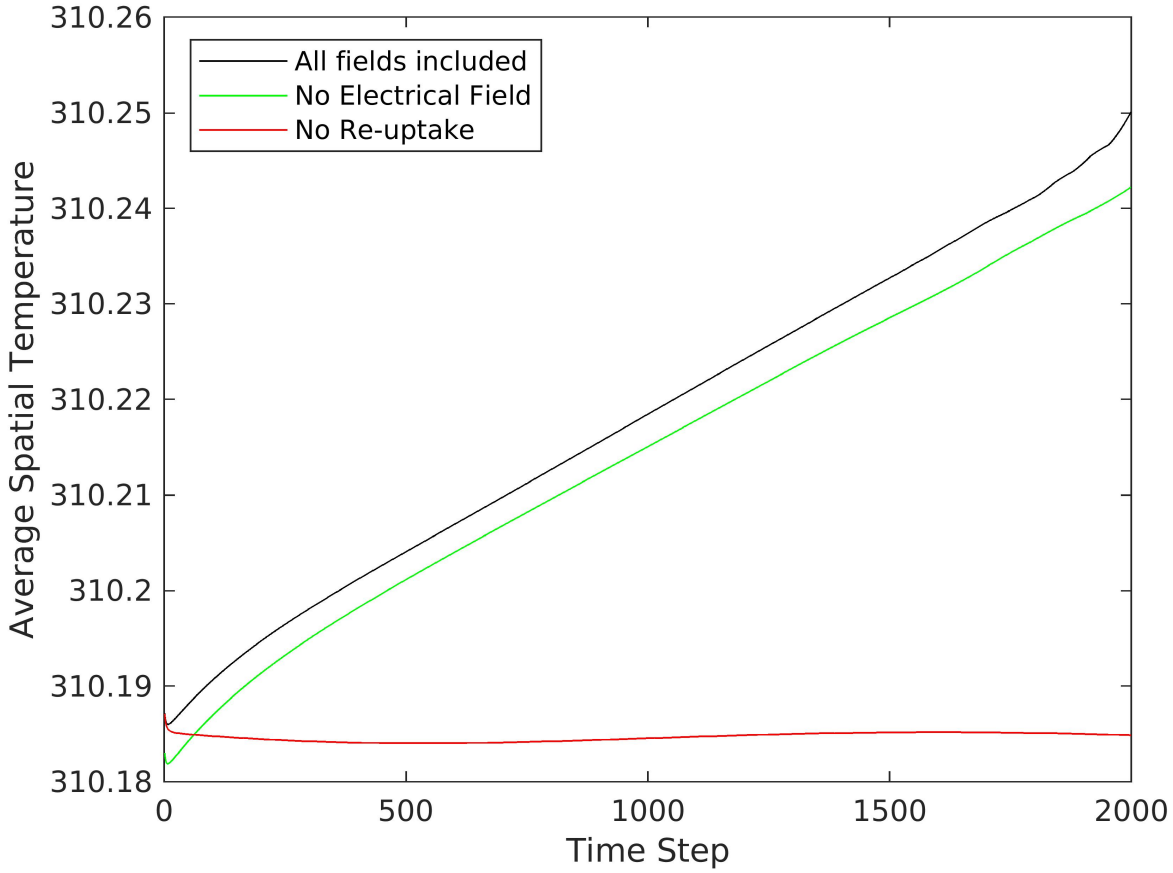

Figure 13: Effects of different fields on evolution of temperature during simulation

The non-linearity at the ending steps of temperature evolution in the case of all fields included is related to **numerical nature of simulations not the physics**. **If we use different mesh and time-step resolution, the non-linearity is going to either flatten or increase**. For example, like in Figure 14, if use 1000 time steps instead of 2000 and mesh size of 0.02 instead of 0.025, the non-linearity increases. This requires the trial and error or deep understanding the relation between mesh size and stability of simulation results.

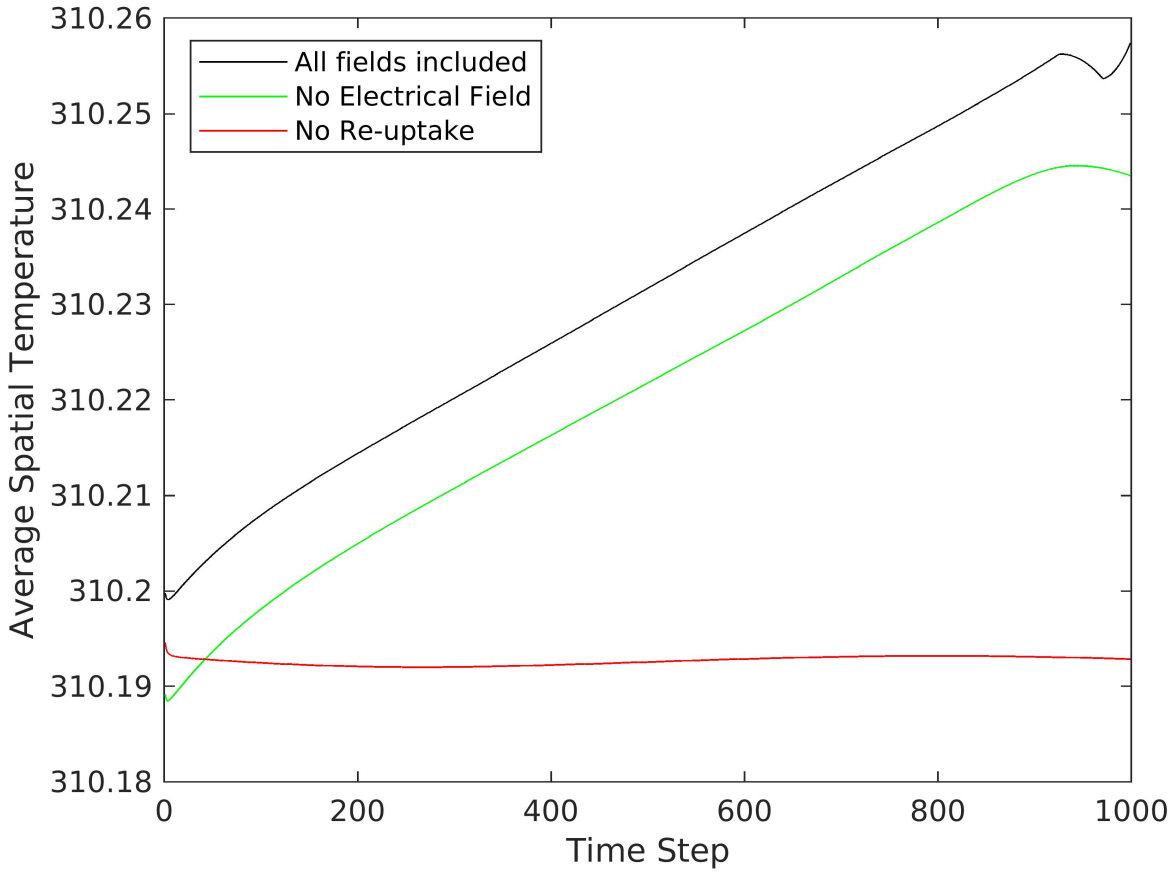

Figure 14: Effects of different fields on evolution of temperature during simulation, case of mesh-size 0.02 and 1000 time-steps. In this case non-linearity increased.

Electrical Field Effect

We have already seen the effect of electrical field on evolution of temperature, which is not considerable. But electrical field has significant effect on distribution of concentration in synaptic cleft.

The goal of diffusion equation is make concentration everywhere equal. So if we run a simulation for concentration solely based on free diffusion with evolution in time, concentration after a certain time-step is going to be uniform in domain, where in we are running simulation, and Figure 15 shows first steps of simulation where concentration is non-uniform. . This is almost identically similar to spatial-evolution of temperature, which we have already shown. In this case also, for our main simulation setup minus the electrical field effect, concentration is going to show spatial non-uniformity until step 33 (we have found this similarly to case of temperature, where we calculated the spatial variance of the related matrix and see when it is going to start to go below 0.0001).

But if we add electrical field effect to our simulations, distribution of concentration at almost every time step is going to be non-uniform. In first 400 micro-seconds due to direction of electrical field, it creates a gradient for particles that pushes them back from moving towards to post-synaptic neuron. Therefore the neurotransmitters are mainly accumulated close to pre-synaptic area. At next 500 microseconds of simulation, as direction of electrical field changes, neurotransmitter accumulate more in post-synaptic area, as electrical field creates directional bias for them in order to move to post-synaptic area. We can observe the results in our simulations in Figure 16.

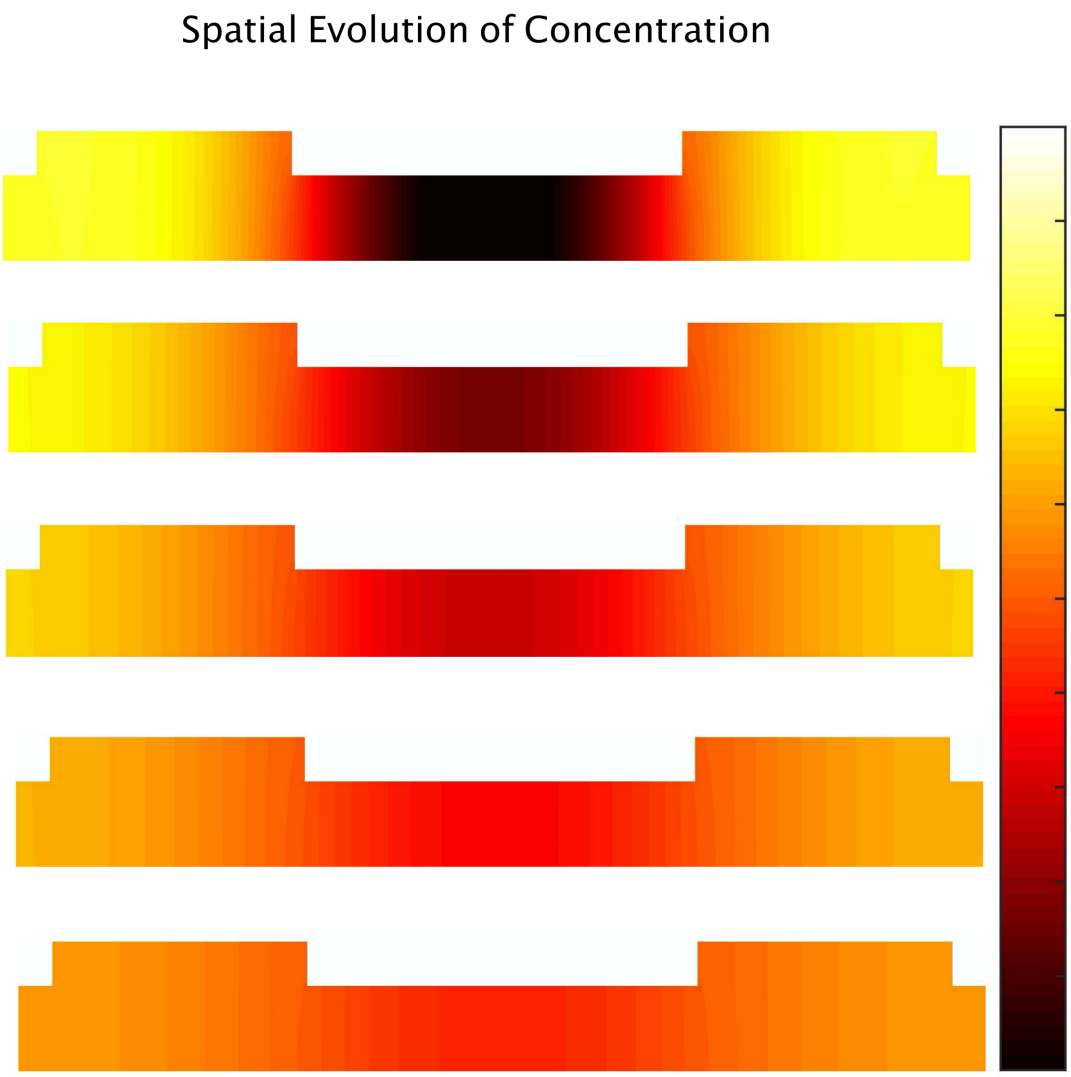

Figure 15: concentration profile of neurotransmitters from up to bottom respectively at steps, 5, 10, 15, 20 and 30. The last step is equivalent to 10 μs in dimensionalized form. The max and min in color bar is 0 and 0.3 and simulations are adjusted to this.

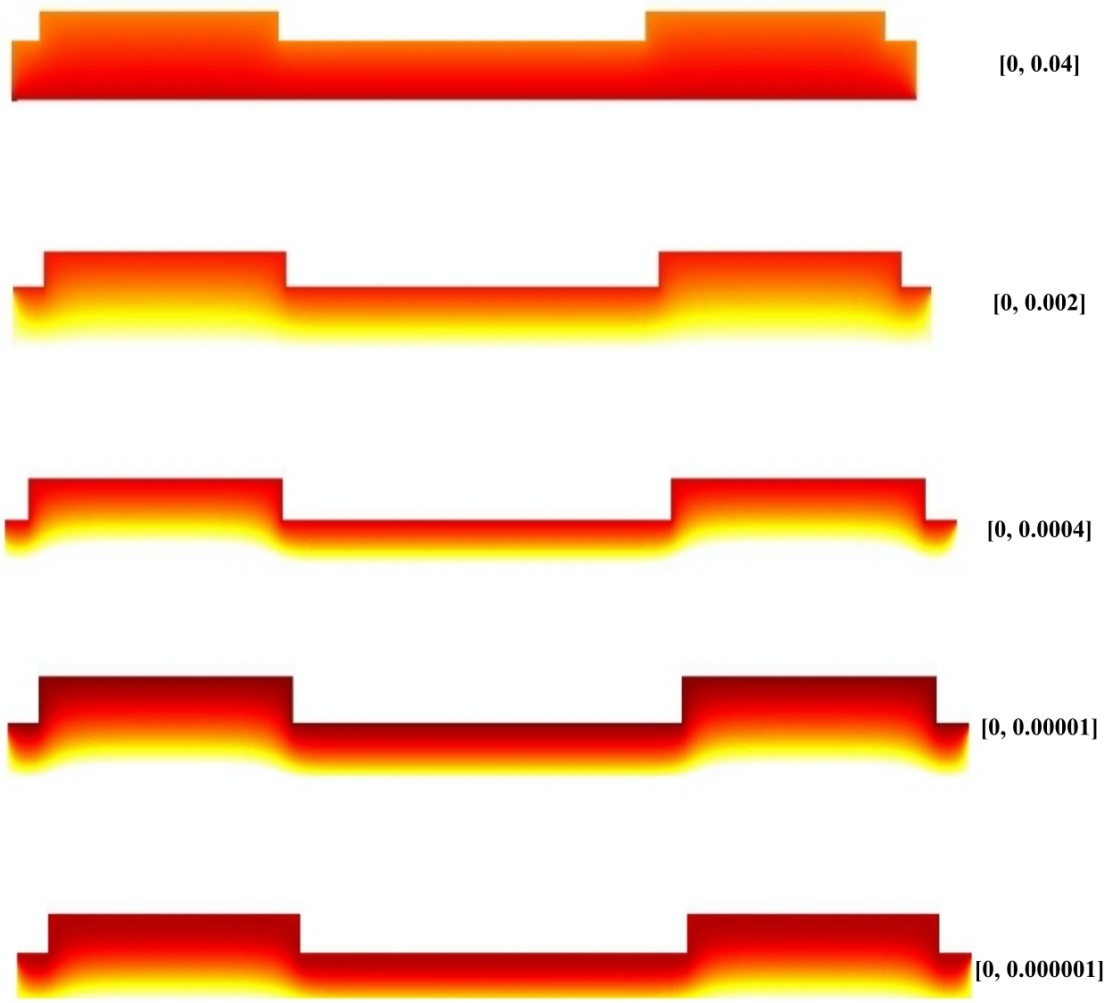

Figure 16: Similar to Figure 15, concentration profile of neurotransmitters from up to bottom respectively at 200, 400, 600, 800 and 1000 micro-seconds. The interval written beside every figure denotes, min and max number of concentration in that time-step of simulation and the color-bar is adjusted to that. Though the concentration profiles are not comparable, we can see more as we go in higher time-steps, concentration is more likely to be accumulated close to post-synaptic area.

5.3 Noise in PDE system

Because of nature of modelling and measurement, it is possible that our system of PDEs 3.1 for modelling the concentration and heat diffusion might not be exact. There might be some source of noise, assuming in concentration, that affects the continuity of the flow in Fick's law. Mathematically simplified, if we have a diffusion equation of following form:

$$\nabla^2 c = \frac{\partial c}{\partial t} \tag{5.3}$$

This equation might not be exact and there might be a source of noise. Noise added this equation is going to be of the form:

$$\nabla^2 c = \frac{\partial c}{\partial t} + \epsilon \tag{5.4}$$

which ϵ here indicates the noise term. Similarly we tried to inject noise (a deterministic source of noise) into our system of PDEs we had before. Unfortunately simulations didn't converge, neither for small nor big values of ϵ.

5.4 Random Walk Simulations

In order to have a intuitive understanding of what's going on in our simulations, in the case of electro-diffusion and effect of electrical field on concentration distribution, we are going to run parallel random walk simulations in order to resemble electro-diffusion. We like to know, whether simulations in the case of macroscopic modelling, which we did so far with the help of fluid mechanics, is going to converge or resemble the case of microscopic modelling, which is the modelling the particles' movement and diffusion as a random-walk. This could give us a green-light that our simulations in case of macroscopic are behaving correctly.

Suppose that we have a particle located at point $x = 0$ on real line, and every τ seconds, it is going to jump l to to the right or l to the left with probability $\frac{1}{2}$. This basic movement is called simple random walk. This simple random walk can be generalized to higher dimension, as a particle moving on lattices with equal probability of movement on every direction. Since in simple random walk, the particle jumps with equal probability in both negative and positive direction, therefore the expectation of particles' location is zero i,e $< x >= 0$. But with some calculation we can compute the variance and standard deviation of particle's dislocation and that would tells us the $\sqrt{< x^2 >} = l\sqrt{\frac{t}{\tau}}$, where t is the time coordinate, we are looking at particle's location. So the displacement after time t is correlated with $\sqrt{t}$. If the the simple random walk had bias for in which direction to jump more, these numbers would be different. For example let's say particle jumps to $+l$ with probability $p > \frac{1}{2}$ and and to $-l$ with probability $1 - p$. Therefore it's more likely to end up in a positive location on real line or mathematically $< x >$ is going to be bigger than 0. Same goes for random walk in higher dimensions.

Random walk is the basis of diffusion equation or in other words discretized version. We can

derive diffusion equation from random walk in following way:

Consider one dimensional case again and we define density particles as $n = \frac{N}{V}$, where V is the volume and N is the number of the particles. n is a a function of time and space so we write it down as $n(x,t)$. If we have to calculate $n(x,t)$ after Δt time passed, therefore we have to consider that particles, which entered location x and particles which left location x and let's say displacement has been Δx a random variable. Therefore:

$$n(x, t+\Delta t) =< n(x-\Delta x, t) >= n(x,t) - \frac{\partial n}{\partial x} < \Delta x > + \frac{1}{2}\frac{\partial^2 n}{\partial x^2} < \Delta x^2 > +... \tag{5.5}$$

From random walk we know particles are equally likely to move left and right, therefore $< \Delta x >= 0$ and that term vanishes. If we expand left hand side with help of Taylor expansion we would have:

$$\frac{\partial n}{\partial t} = D\frac{\partial^2 n}{\partial x^2} \tag{5.6}$$

where $D = \frac{<\Delta x^2>}{2\Delta t}$ is our diffusion coefficient. From random walk we know again, $< \Delta x^2 >$ stands for standard deviation dislocation which is l^2 and Δt is the time between jumps or τ. Therefore:

$$D \sim \frac{l^2}{\tau}, \tag{5.7}$$

That is how free diffusion and random walk are point to the same dynamics and one could reach one equation from another. l in context of statistical physics, also stands for mean free path, which is the distance travelled by one molecule between collisions.

Therefore running a random-walk simulation with mean free path l and time between collisions τ is going to give us results approximately similar to running a simulation for a diffusion equation for a fluid with diffusion coefficient D. In case of diffusion equation, if we have a extra force applied to diffusing particles, therefore in a fixed time-step the particles are more likely to diffuse in the direction of the force applying to them. In their equivalent random walk model, therefore we are dealing with a biased case, where probability of particles jumping in a certain direction is higher than the others.

In our case of simulations in previous chapters, we encountered problem of electro-diffusion. As simulations proceed through time, a strong electrical field appears in synaptic cleft, which its direction is from pre-synaptic neuron to post-synaptic neuron and for glutamate neurotransmitters, which they are negatively charged, it means there is a force pulling them towards post-synaptic neuron. Therefore if we translate this to case of biased random walk, it would mean probability of going towards post-synaptic neuron is higher than going towards pre-synaptic neuron. We are now going to run simple random walk versus biased random walk simulations in synaptic cleft to see effect of electrical field translated to random walk case.

Random Walk Simulations in Synaptic Cleft

We perform single-particle random walk simulations, in Python. The geometry is approximately same as what we had before in case of simulating system of PDEs we had. We use a rectangle shaped area, which high width to height ratio, resembling narrow synaptic cleft. In simulating environment this a 10×200 rectangle, which 10 is equivalent of 20 nm.

We also need to calculate mean free path and scattering time in order to convert to non-dimensionalized version, so we can run random walk steps accordingly. Since we know the relationship between diffusion coefficient and these numbers, and at the same time we know the approximate value for diffusion coefficient of glutamate($\approx 10^{-10} \frac{m^2}{s}$), it is just enough to calculate one of these numbers and we focus on mean free path.

Mean free path is the distance travelled by molecule before the collision, and intuitively it is correlated with number of molecules in unit volume and also the collision cross-section of that molecule. Putting it in a formula is going to be like [25]:

$$l \approx \frac{1}{n\sigma} \tag{5.8}$$

here n is the particle density or number of molecules in a unit volume, and σ is the collision cross section of molecule which is approximately equal to πr^2 which r is the radius of the molecule. Since glutamate is getting diffused in extracellular space, which we assumed is mainly consists of water, therefore we consider n to be the molecular density of water ,but for collision cross section we consider the one for glutamate.

Density of water is $\rho = 1 \frac{gr}{cm^3}$, and molecular weight of water is 18, therefore number density of molecules in liquid water is,

$$n = \frac{N_A}{18} \approx 3 \times 10^{22} cm^{-3} \tag{5.9}$$

We assume that molecular radius is going to be bigger that water molecule, there in order of $1 - 10$ Å, therefore the mean free path would be:

$$l = \frac{1}{n\pi r^2} \approx 0.5 - 1\text{Å} \tag{5.10}$$

So every step in non-dimensionalized geometry is going to be equivalent of 0.1. The scattering time or time between collisions is also approximately $10^{-10} s$.

In general, since our approximation of glutamate density and mean free path might be inaccurate, one solution would be to try run simulations with different values for mean free path. But this task would be futile: for mean free path l, the distance travelled by particles, after N step is going to be a factor of $l\sqrt{N}$. The number N the number of steps for glutamate diffusion and we calculated it according to already know value of diffusion coefficient D. Therefore, the distance travelled inside a geometry, is only going to depend on diffusion coefficient

and for adjusted number of time steps for a certain mean free path, the density is going to look the same, if the diffusion coefficient is the same value. The reason for that is we normalize number of steps always according to diffusion coefficient. Therefore, we proceed with a constant value for mean free path and number of steps. What is going to change the dynamics of random walk, depends on probability vector and boundary conditions.

We base the random walk simulations on single particle trajectories, and repeat this over and over again (1000 times) to get statistically significant results and we experiment with the probability vector of the particle moving in different directions (up, down, left and right).

As for the boundary conditions, we make sure that we particle reaches the left and right ends of the synaptic cleft, it leaves the geometry and when it reaches post-synaptic neuron it stops as a resemblance for binding (Von Neumann and Absorbing boundary condition respectively).

Simulations done in upcoming figures, are accelerated by CUDA, using Numba module in Python.

As far as the probability vector goes we experiment with five different states:

- First three states is dedicated to find a simulation parameters, which resembles the case, where there was no electrical field effect. Therefore in our probability vector, the probability of going down and up is equal. If we declare probability of going up with u and going down with d, therefore $d = u$. We now run three different simulations to to see how density is going to look like. We assume the symmetrical case for probability of going left versus going right. So if probability of going right is r and probability of going left is l, therefore $l = r$. Now we experiment with three different probability vectors:

- $d > l$: In this case we experiment with d almost 3 times bigger than l. We can see results of simulations, in Figure 17. In this case, in a confined time interval, the density is hardly uniformly distributed throughout the geometry, which is not the compatible case with our simulations of PDE model in case of absent electrical field.

- $d < l$: In this case, we experiment with l values 2-3 times bigger than d. We can see results of simulation in Figure 18. In this case density is to a greater extent is uniformly distributed.

- $d << l$: In this case, we experiment with l values 20-30 times larger than d. We can see the results of simulation in Figure 19. In this case, also particles are more or less uniformly distributed, but with more tendency to end up closer to pre-synaptic area.

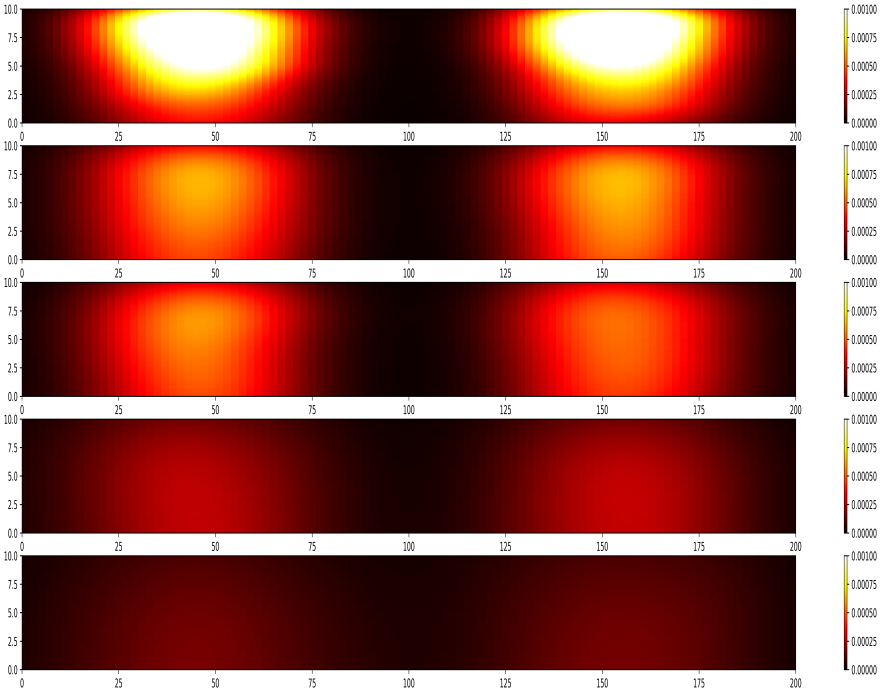

Figure 17: Random walk simulations for the case probability of going up and down is 3 times bigger than probability of going left and right. The density maps from top to down is equivalent to incremental equal steps from 20000 to 100000 steps.

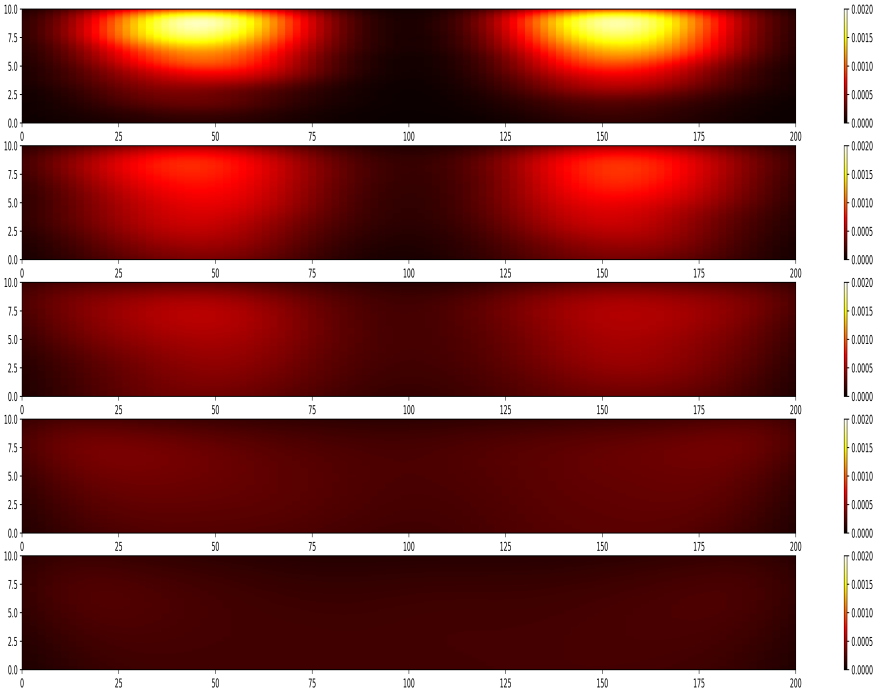

Figure 18: Random walk simulations for the case probability of going up and down is 3 times smaller than probability of going left and right. The density maps from top to down is equivalent to incremental equal steps from 20000 to 100000 steps.

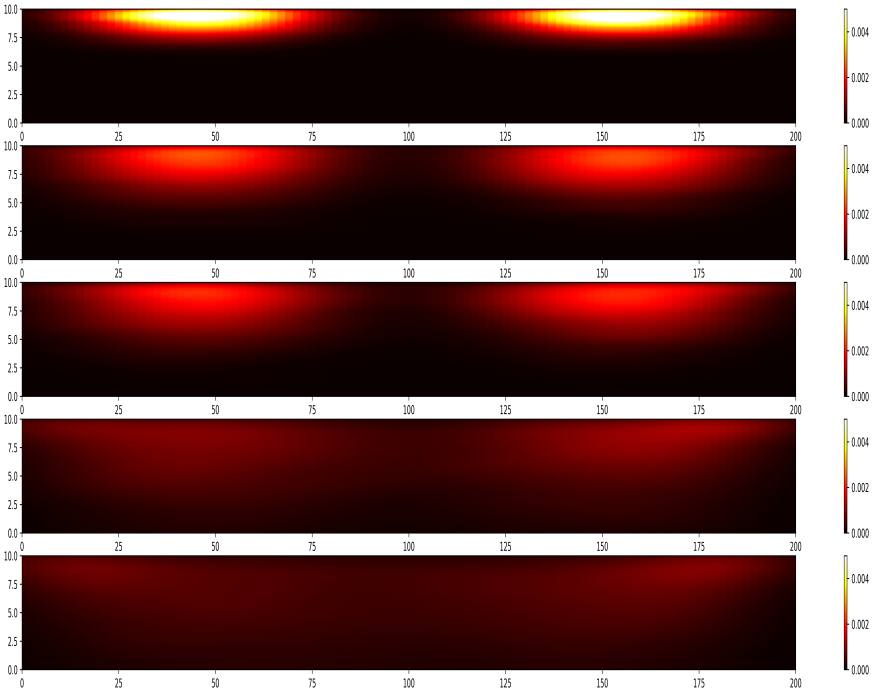

Figure 19: Random walk simulations for the case probability of going up and down is 30 times smaller than probability of going left and right. The density maps from top to down is equivalent to incremental equal steps from 20000 to 100000 steps.

- The next two states of simulations is dedicated to find simulation parameters, which resembles the case of PDE model, when electrical field is present. In simulations of electrical field effect, we have seen the concentration is first accumulated in pre-synaptic area instead of diffusing freely and uniformly in geometry and after a certain period, neurotransmitters start to diffuse mainly downwards and accumulated in post-synaptic area instead of again diffusing uniformly in the geometry. Therefore we assume that, in first cases the probability of going up, u is higher than probability of going down d and the it becomes smaller. We experiment again with two cases and how these probabilities compared to probabilities of going left and right $l = r$. We ignore the case of when l was smaller compared to probability of going up and down, since we have seen in this case simulations tend to very non-uniform and no particle density appears in middle parts of geometry, which in both cases of presence of electrical field and absence of electrical field it is not suited. Therefore we experiment with two cases, when though probability of going up and down, u and d differ, but smaller than probability of going left and right. Therefore, we have two cases:

- $u > d$ in first half of simulations and then $u < d$ in second half and in both cases, u, $d < l = r$. The probability ratio in this case is $\frac{15}{16}$ for the u and d, and when compared to l is 2-3 times smaller. When ratio between u and d is smaller than this value, the density appears to be very fastly accumulated in pre-synaptic and post-synaptic area. We can see results of simulation in Figure 20 . Also in this cases absorbing boundary condition played a big role how concentration is accumulated and reserved when it reaches to post-synaptic area.

- $u > d$ in first half of simulations and then $u < d$ in second half and in both cases, u, $d << l = r$. The probability ratio in this case is $\frac{15}{16}$ for the u and d, and when compared to l is 20-30 times smaller. We can see results of simulation in Figure 21 .

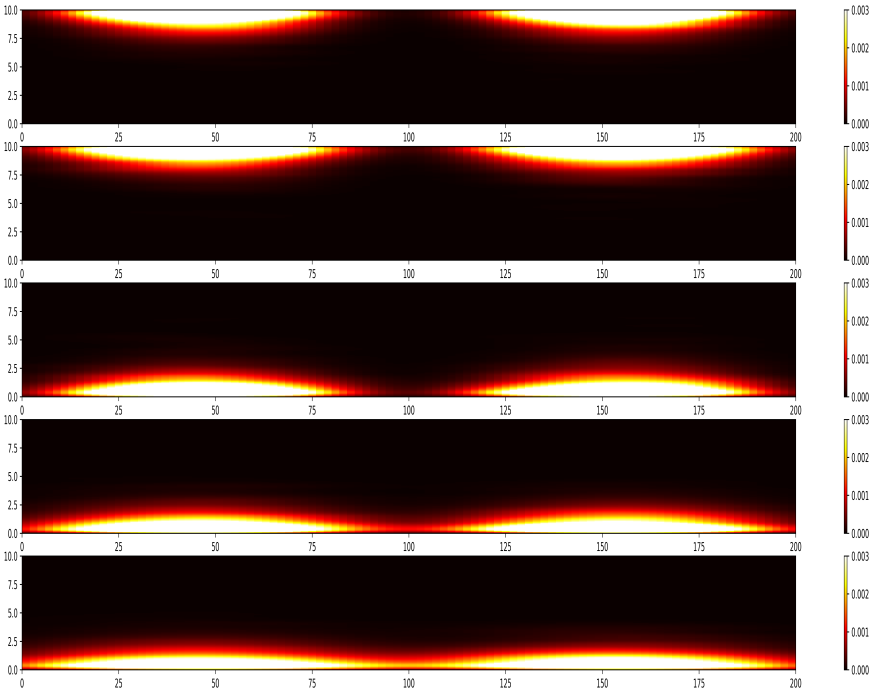

Figure 20: Random walk simulations for the case probability of going up and down is almost 3 times smaller than probability of going left and right. The ration probability $\frac{u}{d}$ is $\frac{15}{16}$ and this is being reversed after 300000 steps. The density maps from top to down is equivalent to incremental equal steps from 200000 to 1000000 steps.

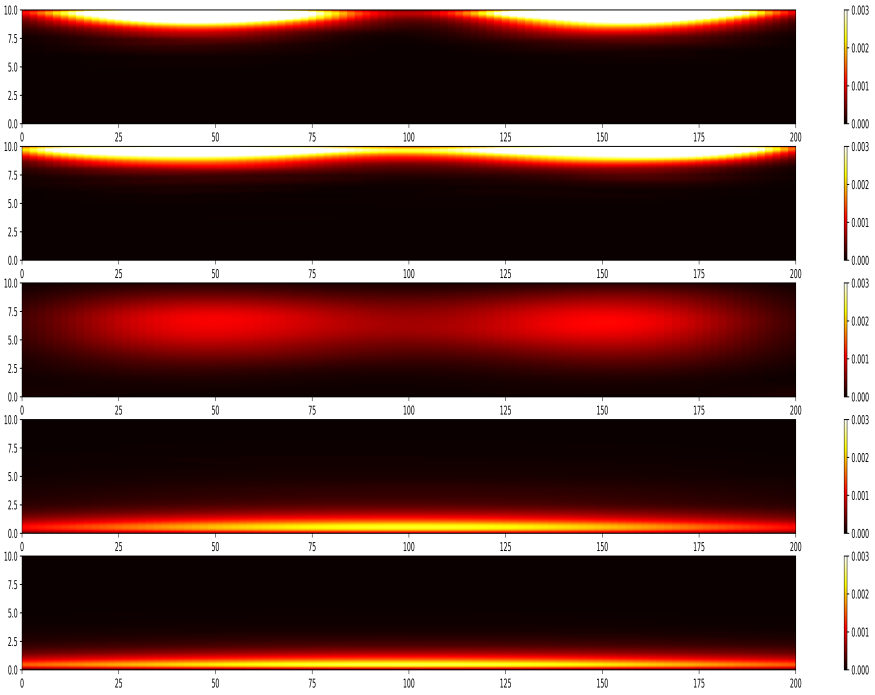

Figure 21: Random walk simulations for the case probability of going up and down is almost 30 times smaller than probability of going left and right. The ration probability $\frac{u}{d}$ is $\frac{15}{16}$ and this is being reversed after 300000 steps. The density maps from top to down is equivalent to incremental equal steps from 200000 to 1000000 steps.

In general, random walk simulations with these parameters resemble the case of PDE modelling. One thing to notice about scale of density in case of random walk simulations vs the case of PDE modelling for concentration. Density here is measured ratio globally i,e number of particles locally compared to total number of particles in whole geometry. This is correlated with concentration values, but they are not the same theoretically. Other thing we can point out is that, the ratio of probability of going down and up and numbers we came up to resemble the uniform diffusion in general seems random. But taking a looking at properties of random-walk we can see that after N step, it covers $\sqrt{N}$ distance on average. Therefore, since synaptic height is 10 times smaller than synaptic width in our simulation setting, therefore probability of going in width compared to height, should be $\sqrt{10} \approx 3$ times bigger to make sure in every direction diffusion is uniform, which complies to the the numerical result we already had.

Chapter 6

Discussion

Through simulations of our simplified model, we have seen that there are possibilities of temperature changes due to neurotransmission in synaptic cleft and these temperature changes showed dependability on factors such as number of times neurotransmitters released, temperature difference between extracellular synaptic cleft and neurotransmitter vesicle content, and chemical potential mixture of those content. Results were summarized in our *heuristic model of temperature change* of equation 5.2. In order to be able to run a comprehensive set of simulations, we had to both simplify model and approximate several parameters, which are not available in literature. We address some of those issues.

The first issue is that, we have assumed to have only one type of neurotransmitter diffusing in the synaptic cleft and this is a very simplified assumption, since usually more than one type of neurotransmitter is being diffused in synaptic cleft. The profile of one synapse can include both excitatory and inhibitory neurotransmitters with different electromagnetic and thermodynamical properties, and therefore their sum effect determines what happens at post-synaptic level.

The whole Onsager system can be applied to consist several type of material mixing together, and it's capable of forming a larger system of equations to encompass this diversity. From that point of view and as a result, we would be dealing with more than a binary mixture. This would lead to a very complex system of coupled equations, which is harder to simulate. But there are tools in physics and mathematics, by which we can possibly simplify a complex combination of neurotransmitter releasing system to a binary mixture.

For example, depending on the question on our hand, we can assume an average or mean field of neurotransmitters diffusing in synapse, instead of several, and work with this average as if there is a single neurotransmitter diffusing. Though they might be different in thermodynamical properties, such as thermal diffusivity and diffusion coefficient, it's highly likely that temperature evolution of their average would be correlated with the original system consists of each neurotransmitter as a different substance. The reason for this hypothesis is that, as we have seen from the simulations, the temperature evolution did not depend on transport properties of the neurotransmitter. This method also works even more realistically, when the different neurotransmitters are releasing from the same synaptic vesicle, since then the initial conditions and source temperature for all neurotransmitter would be same. If they are being released from different vesicles, then again we can work with an average source of initial temperature difference between vesicle contents and cleft. The starting point would be to work with quantity below and write related Onsager relations in a mixture with other

substance such as extracellular fluid or water:

$$c = \sum_k \frac{\rho_k}{\rho} = 1 - \frac{\rho_{sol}}{\rho} \tag{6.1}$$

k here refers to indexes of neurotransmitters, ρ_{sol} is the density of solvent and ρ is the sum of density of whole mixture plus the solvent, which might be the extracellular fluid. As we have already mentioned, if one's considering to work with this average quantity, it should be noted it's better for gaining intuition about the system. Finally, one has to solve the complete set of equations considering each neurotransmitter's concentration separately.

Even working with the whole system, in which each neurotransmitter having a separate concentration diffusion equation, a big question remains and that is in one synapse there are a mixture of excitatory and inhibitory neurotransmitters. Since we are interested in forming action potential and in general electrical activity as a function of temperature change, we want to be able to predict these quantities from temperature evolution. However this is not a trivial task and we mention two cases as an example to illustrate the issue.

First, in case both type of neurotransmitters led to positive/ or negative temperature change, then it would be harder to relate a positive correlation between electrical activity and temperature evolution. The reason for that is, electrical activity of a neuron is sum effect of its pre-synaptic input from its all possible connections and if in the case this mixture is designed in a way that minimizes the electrical activity of post-synaptic neuron, one might expect or hypothesize similarly a minimized temperature change in cleft . But this is not going to be the case, since both two type of neurotransmitters changed temperature in same direction and temperature change definitely not minimized. Second case the vice versa, could predict a correlation between electrical activity and temperature change, if inhibitory synapses/neurotransmitters contributed negatively to temperature, while excitatory synapses/neurotransmitters contributed positively to temperature change with interchangeable sign. This is possible for example, when the temperature of inhibitory neurotransmitter content is smaller than synaptic cleft and it out-numbers the possible temperature increase due to Dufour effect and entropy increase that we already talked about.

Author's proposed solution measuring temperature in synapses with pre-existing knowledge that they are either inhibitory or excitatory. After that, and seeing their total effect on post-synaptic neuron, one can build a model combining the temperature evolution of both type of synapses to predict the electrical activity.

In general, there are always room for more complex and twisted interplay of different type of neurons, synapses, receptors, neurotransmitters and etc. However, if the the concept and general method is valid and the possible experimental methods invented to facilitate measurement, it is highly possible to model to these complex interplays. Therefore more data is needed in order to make better models and hypothesis. So far the only hypothesis we can make is our *heuristic equation*.

After possible establishment of experimental methods and how to differentiate between excitatory and inhibitory responses in temperature measurements, one might be interested looking for more clinical applications. For example, it's hypothesized and studied that Epileptic activity at molecular level, is a result of imbalance between excitatory and inhibitory conductances. Seizures or Epileptic activity can be induced/blocked by blocking/activating inhibitory/excitatory conductances [36]. As already mentioned, if it's possible to differentiate inhibitory and excitatory responses from temperature measurement time-series, one would be able to find the possible correlation between local, microscopic level electrical activity in abnormal Epileptic cases and temperature measurement time series. This is a very generalized proposition, which indicates a possible clinical application of temperature measurements that could explain possible local temperature alterations in such clinical cases. But overall the author does not hypothesize a formulation of the problem, as the mechanisms of inducing imbalance of inhibitory and excitatory responses are significantly diverse and one not might be able to formulate a single method to study the correlations [37].

Other question arises, as we have mentioned in the introduction of thesis, there was some experimental study, in which the authors observed intracerebtal temperature alterations in focal seizures [12]. Even though, this study was mentioned for further motivation of the thesis, one might ask the question is there possibility of explaining temperature changes mentioned in the study through our framework? First, one has to consider the fact that in this study temperature measurements has done by thermocouple and spatial resolution of thermocouple temperature measurement is in order of millimeter to micrometer. Therefore nothing can be said about our predictions in case of sub-micrometer and nanometer. The authors also induced focal seizures with different mechanisms, and observed that local brain temperature changes is more correlated with increase in cortical blood flow, independently of neuronal activity. Therefore one might refer to Yablonskiy's initial theory of local brain temperature change due to blood-flow to test and explain the hypothesis.

We also mentioned in the abstract the possibility of intracleftic temperature change during short term synaptic plasticity and long term potentiation, specifically the early phase (eLTP). The assumptions about mechanisms of short term plasticity and eLTP have in common are, the increased probability of vesicle binding and release [7][39]. As we have seen before in simulation results and our *heuristic equation*, more content release would mean more temperature change. Therefore one might hypothesize of consistent increase or decrease of temperature in synaptic cleft (depending on parameters and initial condition) during short term plasticity and eLTP. eLTP might have another mechanisms of induction and is not limited to content release of vesicle. Therefore, this hypothesis would be limited to the case this assumption is proved to valid.

In general the simulation results as we have already mentioned, they correlate to number of neurotransmitter release from a releasing site and other parameters, and in previous point we tried to suggest how to interpret these results corresponding to other established concepts of electrical activity and related measurement methods. Most important issue would be measurement of temperature itself. Existing methods such as gold-coating, nano-diamonds and nano-particles, as temperature contrasting agents, barely can be applied to measure temper-

ature in small spatial scale of synaptic cleft. Hypothetically, in future and with possibility of advancement in measurement techniques and enhancement of resolution, there are factors should be considered to to design an experiment, which can falsify or validate results of this thesis. First and foremost, there should be a method for measuring temperature at a release site or inside of the synaptic vesicle, which was a predicting factor in final temperature change. Similarly the temperature of synaptic cleft, should be measured in the case when there is no neurotransmissision to find the baseline temperature. The temperature difference between this two quantities is predicting factor of the final temperature change.

Secondly, there should be a method for measuring how many times synaptic vesicles bind to releasing site and release their material. Therefore a real-time measurement of this quantity is needed. However it's possible that due to nature of certain microscopy techniques such as electron microscopy, the sample should be fixed and this hinders the measurement of real time vesicle binding and release.

Nevertheless, if in some hypothetical situation one is able to measure some data about vesicle binding and release, the times series measured from synaptic cleft during neurotransmission can undergo a statistical inference to validate the model. In the case finding correlation between electrical activity and temperature change, one should consider the the first point we made about complex interplays of neurotransmitters. The author has not put any concrete numerical prediction about inferring electrical activity from temperature changes and this task must be modelled and hypothesized before such experiments.

In our simulations, we assumed a constant simplified geometry for the model. The reason for this task is the almost non-existing simulation tools for a geometry that the boundaries show movements and change. This is the case in neurotransmission, since it's believed that synaptic vesicles bind and fully fuse with membrane, therefore the whole synaptic cleft geometry would show a dynamic boundary in the whole process. In cases where kiss and run fusion happens, (type of neurotransmission which there is no full fusion of vesicles and vesicles separate from membrane after releasing content), the simplified geometry can be realistic. Even though, kiss and run is a rarer form of neurotransmission compared to full fusion. Whether or not the temperature evolution depends on this factor, is a hard question to answer. But one can approximately predict since, the difference between two cases at two extreme is about addition of a volume as big as synaptic vesicle and synaptic vesicle is smaller compared to whole cleft, there probably the whole effect might be negligible. One the other hand, if one is interested in diffusion and concentration dynamics of neurotransmitters, then one can hypothesize of a non-negligible effect in movement of neurotransmitters.

We have assumed, when developing our model, that there is no existence of bulk flow and main movement of neurotransmitters governed by diffusion. The interpretation of this could be that, a huge chunk of neurotransmitters are not going to move in one similar direction, rather they would have their own random direction governed by thermal motions and other thermodynamical gradients such as temperature gradient, which doesn't lead to bulk flows. However, there is a possibility, when synaptic vesicle fusing with membrane, this moving membrane wall of vesicle is going to give an initial momentum to neurotransmitter

molecules. In this case, there is a possibility of induction of bulk flow in neurotransmitter molecules. Therefore one has to solve, Navier-Stokes equations for determining the bulk flow dynamics and how it gives rise as to a conductive force of neurotransmitter molecules. Determining initial conditions, for this case, is a challenging task, and it should be accompanied by Molecular Dynamics simulation of vesicle fusion and SNARE-protein complex dynamics. Making a detailed hypothesis and road to experimental for this, is out of scope of this thesis. However, studying the difference in synaptic delay time course between synapses, which operate on kiss and run diffusion versus full fusion case, would be the possible first step to investigate this aspect of neurotransmission.

Regarding parameters of the model, we assumed lots of simplification. For some parameters such as chemical potential, we assumed we are dealing with water as the solvent. However, the synaptic cleft has more complex content with lots of other macromolecules. The question would be how is this simplification affects temperature evolution predictions? The chemical potential mixture showed its presence at Dufour effect, which represents the diffusion of temperature due to mass diffusion. It can be interpreted a moving mass brings along heat. Explicitly, the term was $\frac{\partial \mu}{\partial c}$, which here μ is the chemical potential of the mixture and c is the concentration of the neurotransmitter.

Another simplification was, considering ΔT_0 identical and equal for every time vesicle release their content. Mainly this came from the fact all vesicles originate from intracellular space and might have same temperature profile. However, it's possible that vesicle membranes provide insulation and therefore gives independent temperature profile to every vesicle. ΔT_0 also might differ according to previous times of release, since every release adjusts baseline temperature in cleft. Therefore, ΔT_0 would have more complicated form as a function of $N-1$, number of times released before and total Dufour effect δ. Therefore, one can predict decline of ΔT_0, through time and therefore reaching a point of saturation as ΔT_0 might converge to zero. In that case, it would be harder to make a detailed hypothesis with parameters of number of release and Dufour effect, but also that doesn't falsify the possibility of overall temperature change in cleft during neurotransmission. More powerful simulation packages needed to form more complex source function with variable ΔT_0, as in our framework with more complex forms, the algorithms didn't converge to give the comprehensive solution. This task can be delegated to a future research. However, we can make some analytical approximation for convergence of ΔT_0. From equation 5.2 we know that α was the linear coefficient determining proportion of temperature after release with ΔT_0 difference. It means for example if temperature difference between vesicle content and cleft was 1 Kelvin, therefore after release temperature of cleft would rise by α Kelvin. Now, if temperature difference between cleft and vesicle before was ΔT_0, it is now reduced by $\alpha \Delta T_0$. Therefore, after second release temperature would rise by $\alpha(1-\alpha)\Delta T_0$. By induction, after N release the temperature difference between vesicle content and cleft would be $\sum_{i=1}^{N}(-1)^i \alpha^i \Delta T_0$. When N converges to infinity, this would be equal to $\frac{1}{1+\alpha}\Delta T_0$. In chapter of simulation results, our simulation results had $\alpha \approx 0.1$. Therefore, at infinity the temperature difference between vesicle content and cleft, would be around $\frac{10}{11}$ of initial temperature difference. In other words for small α, the original hypothesis can be normalized with the computed value and still can be regarded as valid to some degree. We neglected Dufour effect δ, since regardless

of constant or non-constant ΔT_0, it is embedded in our equations naturally and there is no need for complex modification in source terms.

We assumed some simplification that states we are dealing with an ideal solution. Ideal solution here states, that on microscopic level molecular interactions between two components are negligible. Therefore the chemical potential of the mixture, would be the linear combination of the chemical potentials of the two components at local level. This assumption is also compatible, when we moved away from modelling this problem with Boltzmann equation and the assumption that we neglected chemical and physical profile of molecular collisions and how they possibly might contribute to heat dissipation. Therefore the chemical potential mixture was simplified to $\mu = \mu_1 - \mu_2$, which μ_1 and μ_2 are respectively chemical potential of the neurotransmitter and the solvent (water or in general extracellular fluid) normalized per mole. As we have mentioned in the introduction of the thesis, one of the motivations for looking at temperature of neurotransmission was the idea the in this mixing process, broadly speaking, the entropy of system increases and this might lead to heat generation. This idea manifests itself in our model in Dufour effect and the chemical potential of the mixture. Indeed, if there was no difference between synaptic vesicle content and extracellular fluid, $\mu = \mu_1 - \mu_2$ would be equal to zero and the Dufour effect would be neglected.

As we have seen, in results of the simulation, even if assume there is no temperature difference between synaptic vesicle content and extracellular component, after mixture the the temperature of the solution increases nearly 30 mill-Kelvin and this indicates the temperature rise due to difference in chemical potential mixture of two content. 30-40 milli-Kelvin might seem random at first glance, but this mainly depends on simulation setup, geometry and PDE parameters, which in this case are molecular mass of glutamate and water in expanded version of chemical potential mixture, which comes from statistical mechanics. There might be possibility that this ideal solution assumption might be incorrect and in that case, the chemical potential of the mixture would have a complicated form and higher order terms. It's not clear even in that case one would be able to form balance equations, as complicated terms arises. Another issue we can note that simulations were done in 2D due to time-limit and less complexity. Similar equations can be simulated with related parameters in 3D and highly likely the simulations were going to give us similar results. Nevertheless, the author acknowledges the validity of the model up to these assumptions.

There are other parameters we assumed to be constant or equal throughout the simulation, and there are possibilities of the otherwise. We assumed that temperature of the synaptic vesicles are equal in every release. This might not be true and synaptic vesicle content might show variability in that quantity. Another quantity that was assumed to be constant, was thermal diffusion coefficient k_T and we used some already experimentally observed patterns, that this number of mixtures lies between $10^{-2} - 10^{-3}$. Theoretically speaking, this values depends of variables of the simulation such as temperature and concentration and takes a complicated form. Using highly nonlinear form of this k_T, would complicate the simulations and assumingly it's not playing a big role in the question we were more interested and that was temperature dynamics. k_T manifests itself in Soret effect, which is diffusion of mass in direction of temperature gradient and as a matter of fact it, there should be a

significantly a big temperature gradient for Soret effect to be observable. This is usually the case in problems of geothermal nature and it's very rare to non-existent in biology. In general simplifications or assumptions we made doesn't hurt the general principles, that we are looking for build upon our models of temperature evolution and how it can be useful in neuroscientific and biological contexts.

Another simplification we made, was assuming some constant values for initial conditions and boundary conditions. These values can again get more complicated forms having parameters depending on neurophyiological properties of cleft. For more complicated cases of these values with complex function forms, simulations tend to jam, which can be attributed to nonlinearity of our PDE system. In general, again more powerful computational packages needed to handle the complexity.

As we have already mentioned in previous sections, one might be interested in temperature dynamics in bigger brain regions such as a neurovascular unit, or non-synaptic regions where neurotransmitters diffuse away from intracleft and being reuptaked by Glial cells. This interest becomes more apparent, especially when there is no experimental method to look at synaptic cleft's temperature and one might be interested in getting information in a little larger spatial scale temperature dynamic to infer something about temperature changes synaptically. In this case, two things should be considered: First, we limited our simulations to cleft. One might take a bigger geometry, as big as possible area which could contain possible area which neurotransmitter can reach by diffusing away from synapse. Not clear, but possible due to Dufour effect neurotransmitters would carry away some heat and cause temperature dynamic change extra-synaptically. Synchronous synaptic activities would also play a big role in bigger scale modelling and timing would be very important.

Second, one should consider what is possible molecular processes going on in bigger area. If they have considerably bigger scale, they can be confined with Onsager relations and make a case of mass-heat diffusion, like we already did for glutamate.

Other possibilities could be, as done in previous research of similar topic, temperature change due to metabolism and blood-flow regulation. Combining all these altogether and measure the temperature, one can get a time series. From spectral analyzing the time series,it would be possible to infer what is the contribution of blood flow and what is the contribution of other processes to temperature in bigger scale. One reason for possibility that this hypothesis could work is that, different processes occur with different temporal frequencies and therefore possible that their temperature contribution would show a distinctive frequencies in such time series. The reason for mentioning time series, as a format of recorded temperature data, is the assumption of continuous recording of temperature with small time-steps. Instead one can have a single-time temperature recording, but then one should pay attention to hypotheses we made regarding the relationship between temperature change and other variables such as number of release and etc.

The results for electrical field effect depends on what kind of boundary conditions we put for electrical potential in our equations. Neurophysiologically speaking, this means time evo-

lution of pre-synaptic and post-synaptic membrane potential. The reason that there is an existing electrical field in synaptic cleft, as we have already mentioned is the synaptic delay, which represents the the time course that it takes for action potential or electrical activity in general to propagate to post-synaptic neuron. There are several issues that should be noted. As we already mentioned, we used a simplified form of synaptic delay for Ionotropic receptor. For Metabotropic receptors, the synaptic delay in general is more prolonged and the electrical activities of pre- and post-synaptic neuron would have different functional form. Second, we assumed the firing of second neuron merely depends on one pre-synaptic neuron. This is not realistic, since a neuron gets synaptic input from many neurons and their sum determines fate of neural activity the neuron and again this would lead to more complex form pre-synaptic and post-synaptic neurons membrane potential and as a result a more complex boundary condition for our problem. But in general this doesn't deteriorate the assumption of existing synaptic delay and how we built our simulations based on that, the author acknowledges that the complexities should be considered when approaching experimental testing.

Last but not least, one thing that should be noted and we didn't include in our modelling, is the fact the binding of neurotransmitters to post-synaptic neuron play a CAUSAL ROLE in inducing electrical activity. In our coupled system of PDEs, it is treated as if they are separate phenomenon. It's mathematically not possible to have such model in context of partial differential equations. Suppose that we denote membrane potential of post-synaptic neuron as V_{post}. Therefore, as we have said that about causal relationship of neurotransmitter concentration c and V_{post}, would make V_{post} as a function of c, written $V_{post}(c)$. This cannot be integrated in our PDE system since, the boundary conditions should defined in advance and shouldn't have dependency on functions we are trying to solve through numerical or analytical methods. Another framework is needed to address this problem. Though qualitative observation from our simulations, we have seen that there is a significant difference, how diffusion of neurotransmitters represented between the cases where electrical field was absent and electrical field was present. Whether or not this is going to be the case again, when the mentioned causal relationship considered is a question must be investigated. Another issue that should be noted is that electrical field affects neurons with existing non-neutral electrical properties. Either they are charged, or have non-zero dipole moment. For neurotransmitters which belong to non of these categories electrical field doesn't have any impact.

As have talked about neurotransmitter binding to receptors, the question arises whether this phenomenon can have impact on temperature dynamics? Ligand binding is a microscopic phenomenon and diffusion of materials in general mesoscopic to macroscopic. Ligand binding in general is associated with free energy change and this might lead to local disturbances of entropy and as a result heat dissipation and temperature changes. There are possibilities that how can model the effect of ligand binding on temperature changes. One might treat the free energy changes and associate them with entropy balance equation. These might appear as source functions in entropy balance equations. In simulating to see the effect of situation, binding kinetics is going to play big role as they indicate the scale of free energy change, by pointing out how many times ligand binding happens and etc.

It's also worth noting some issues about validity of assumptions our model was based upon, i.e non-equilibrium thermodynamics. So for in neuroscience literature, it's commonly accepted that neurotransmission is a diffusion phenomenon. Therefore, the continuity assumption about the nature of flows in our framework is consistent with previous modellings of neurotransmission as diffusion phenomenon. However, more validation of this assumption is required and considerable expertise needed to check whether the problem is in the limits of hydrodynamics.

Similar question arises whether we can use the Onsager framework at all. Onsager framework assumes that system is not far from equilibrium and reaches equilibrium pretty fast. That's why we can expand thermodynamics fluxes as a linear function of thermodynamics forces, i.e the temperature or concentration gradients. There is no data on relaxation times of thermodynamical processes in intracleftic scale. Biological systems overall considered to be far from equilibrium, but this assumption varies from compartment to compartment. Intracellular environment is pretty much far from equilibrium compared to other compartments [3]. The reason for that is existence of molecular motors, which makes relaxation time of thermodynamic processes longer. In synaptic cleft, this diversity is less apparent. In general, in order to investigate whether this assumptions might be correct, one can run similar experimental methods to check the validity. In 1961 [38], several experiments have been conducted to verify Onsager relations, which finally brought Nobel Prize for Onsager in 1968. Conducting similar experiments in synaptic cleft requires the experimental methods to both control and measure temperature in intracleftic dimensions and therefore limited to up to advancement of temperature methods in that area. The interested reader is referred therefore to [38] for more detailed instructions for running such experiments.

Another powerful aspect of Onsager framework is that, it can be extended to include chemical reactions. Chemical reactions can contribute to diffusion flux, heat flux or any other flux that can have similar tensorial character. In our case, we simply used re-uptake and degradation as a source term in the equations, as a factor of concentration, $\alpha\ c$, which α is the proportion of neurotransmitter being degraded or re-uptaked. Depending on type of neurotransmitter and what type of chemical reactions it is participating in, it can be included as Onsager coefficients of concentration. We expanded previously diffusion flux as $J_k = D\nabla c + k\frac{\nabla T}{T}$. Therefore another term of related to chemical reactions can be added into this as the form $R_k(t)$, which $R(t)$ here the amount of material produced and destroyed in chemical reactions. Writing down diffusion equation with reactions considered, finally going to give us famous reaction-diffusion equation. Coupling thermal diffusion with chemical reaction is a bit more complicated, as the amount of heat production or free energy change should be coupled with temperature diffusion and give rise to complexity.

We have found some parameters for random walk setting to have an understanding whether it's possible, qualitatively speaking, to regenerate the results of effect of electro-diffusion at microscopic level. We should note that, even though some parameters have been found the quantitative comparison is not possible. In expanding of random walk density function, we could recover diffusion equations by ignoring higher order terms of random-walk density

function. In general also random walk simulations refer to single particle trajectories repeated many times. In reality we have simultaneous particles diffusing in Brownian manner and as we have mentioned introduction, one needs to solve Boltzmann equation to account the collision between an ensemble of molecules diffusing together. That's the only way to have an quantitative comparison of our results at microscopic level.

Due to lack of computational power, we couldn't see what would happens when introduce a noise terms when simulating our model. This would be important when some measurement method introduces heat flux into system. Due to nature of equations, this heat flux addition is not going to be subtracted by linear methods, since a heat source diffuses in a non-linear fashion. Therefore this crucial step should be studied through more powerful package of finite elements, which can handle noise term introduction.

Finally, we can address the main essence of the thesis; with technical calculations we showed that we can attribute temperature change to lots of molecular processes due to two factors: First is the Dufour effect, which gives us the tool to calculate temperature propagation due to mass movement and chemical potential mixture . Second, is that due to spatial temperature heterogeneity, any mass movement between two points of different temperature profile, would give rise to measurable temperature fluctuations. Interested reader can think of any contexts in biology and neuroscience, which therein these two points can give us the the tools of predictability and measurability for the on-going process.

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