Applied Mathematics in Neuroscience

Prof. Dr. Gillian Queisser

1. September 2017

1 Introduction

1.1 Content of this course

1. Biological foundation
2. Translation into theoretical neuroscience
3. Translation into mathematical models
    a) based on ordinary differential equations (temporal dynamics)
    b) based on partial differential equations (spatio-temporal dynamics)
4. Solving model equations
    a) reconstruction methods
    b) discretization methods
    c) numerical solvers
5. Applications

Note: Biology and numerical mathematics will remain incomplete! Consider courses that focus on applied mathematics and numerical/computational methods, as well as additional interdisciplinary courses.

2 Fundamentals of Neurobiology

2.1 From genes to behavior

The brain is all about scales, temporal and spatial. Coupling scales allows for large scale information processing.

- Molecular scale (biochemical experiments)
- Cellular scale (electrophysiology, single cell recordings, imaging techniques)
- Small networks, e.g. micro-circuits (electrophysiology, single cell recordings, imaging techniques)
- Network scale (multi-electrode arrays)
- Brain regions (MRT, EEG, ...)
- Behavior (empirical studies)

Research is typically designed to study single scales. Studying the coupled multiscale system is the holy grail.

2.2 Neurons

Cell theory

Is the brain a topologically connected network, or does it consist of single entities that can communicate with each other?

The Golgi-staining method (1885) gives an answer: potassium dichromate + silver nitrate reacts to silver chromate inside a cell. This leads to staining of *single* cells in a network and the visualization of these elementary entities.

2.2.1 The plasma membrane

The plasma membrane is the defining part of a cell. It separates the intra- and extracellular space with the help of a bilipid structure.

Plasma membrane ingredients:
55 % proteins

25 % phospholipids
13 % cholesterol
4 % lipids
3 % carbohydrates

Proteins are the building blocks for membrane embedded channels (passive + active), through which ions can be selectively exchanged between the intra- and extra-cellular space. This is a central feature in modeling cellular processes.

2.2.2 Dendrites

- branched cable structure, tapered away from the soma
- passive membrane properties (signal amplitude decay during signal propagation)
- dendrites receive signals from connected cells
- dendrites communicate towards the soma and axon

2.2.3 Axon

- similar structure than dendrites, but typically small cable diameter
- active membrane properties (no amplitude decay)
- myelin-sheathed cable (glia cells) leads to increased signal propagation
- signal initiator at cell contacts

2.2.4 Soma

- The soma contains the cell nucleus, endoplasmic reticulum, and other organelles, such as mitochondria and golgi apparatus
- largest part of the cell with respect to cell volume
- connects dendrites and axon
- filled with cytosol (intra-cellular fluid)

2.2.5 Cell nucleus

- located in the cell soma
- bounded by double bi-lipid-membranes (nuclear envelope). The outer membrane is a continuation of the endoplasmic membrane (see endoplasmic reticulum)
- harbors the DNA

- nuclear pore complexes connect the cytosol and intra-nuclear space, through which ions and larger molecules can pass, in order to activate survival relevant processes
- at the nucleus DNA is transcribed to produce proteins for membrane channels, receptors etc. (cellular plasticity)

2.2.6 Endoplasmic Reticulum (ER)

- outer nuclear membrane extends into ER membrane
- rough ER: synthesis of proteins
- smooth ER: production of lipids, fatty acids and calcium storage
- large calcium store: ER membrane enables bi-directional exchange of calcium ions between cytosol and intra-ER compartments (SERCA pumps, IP3-receptors, ryanodine receptors) → Calcium Induced Calcium Release (more details in later section)
- the ER reaches far into the dendrites and axon (cell-within-a-cell geometry)

2.2.7 Mitochondria

- energy source: via a highly infolded inner membrane a proton-gradient is established. This enables ATP-production (e.g. citric acid cycle)
- calcium store

2.2.8 The cytoskeleton

The cytoskeleton is the transport network (highway system) of the cell. It is constructed by dynamic *filaments*.

One dimensional structures: microtubules

- 20nm diameter
- motor proteins move molecules, vesicles, and organelles along microtubules

Two-dimensional structures: actin and neurofilaments

Polymerization of actin produces a 2D matrix which typically is connected to the cell's plasma membrane. This matrix also stabilizes the cellular morphology. *Neurofilaments*

1. form the nuclear lamina (connected to the inner membrane of the nuclear envelope)
2. attach the DNA
3. stabilize nuclear morphology

Three-dimensional structures

A combination of 1D and 2D cytoskeleton compounds create a 3D infrastructure that allows targeted dispatch of molecules, vesicles, and organelles to distinct intracellular locations.

2.3 Connections between neurons

When and how do neurons form connections?

Recap: axons are signal propagators, while dendrites receive input. ⇒ axons and dendrites need to have distinct contact points. Thus, contact can only be accomplished through spatial proximity.

2.3.1 Gap Junctions

In areas where nerve fibers run densely and parallel, gap junctions can form whenever axons/dendrites come into close contact (2-4nm distance).

Gap junctions

- are protein complexes that allow direct trans-cellular ion exchange
- very fast signal transmission
- low *selectivity* during signal transmission

Q: Why died the density of gap junction decrease along the evolutionary chain?
A: The reason seems to stem from low selectivity in signal transmission: gap junction coupled cells will operate in unison which leads to a strong reduction in complexity. To increase complexity the brain has a second type of cellular coupling.

2.3.2 Chemical synapses

Chemical synapses have an intricate architecture for transmitting signals from one cell to another. Cells are not connected geometrically (synaptic cleft). For signal transduction multiple things need to happen (increase in complexity). Chemical synapses are categorized in terms of the type of neurotransmitter that is released during signal transduction. Roughly these neurotransmitters are either inhibitory or excitatory.

Presynapse

- Neurotransmitters reach the presynaptic bouton via the entry from the extracellular space or the axon

- Vesicles are filled with neurotransmitters from the intracellular space. The vesicle membrane further has the capability to synthesize neurotransmitters from pre-transmitter compounds.
- Neurotransmitter-filled vesicles move to the presynaptic membrane

Exocytosis

Once a vesicle is located at the presynaptic membrane, the vesicle membrane can fuse with the presynaptic membrane. This occurs when an electrical signal changes the membrane potential (see later sections), which in turn activates plasma membrane located calcium channels triggering membrane fusion (Omega-formation). This leads to release of neurotransmitter into the synaptic cleft.

Endocytosis

Conservation of mass with respect to vesicle density requires production of vesicles that balances vesicle exocytosis. This process is called *endocytosis*. From fused vesicle membrane material, in which all relevant protein complexes are available, new vesicles are synthesized in the vicinity of the *active zone*, i.e. the vesicle fusion zone. The synthesized empty vesicles are gradually filled with neurotransmitter (recycling process).

Signal transduction through the synaptic cleft

- released neurotransmitter diffuses to the postsynaptic membrane
- postsynaptic receptors are activated by neurotransmitter
- ion-specific channels open
- membrane potential changes in postsynaptic cell
- signal transduction in postsynaptic cell

2.4 Cerebral cortex

Roughly the cortex can be categorized into

1. primary and secondary sensory cortex
2. primary and secondary motor cortex
3. association cortex (language, information processing, learning, ...)

Hippocampus

1. involved in learning and memory
2. planar structure, and as such well accessible to experimental science

2.5 Electrical properties of neurons

Ion channels in the plasma membrane allow selective ion exchange between intra- and extra-cellular space. The exchange takes place along concentration and voltage gradients. *Ion pumps* work against these gradients (energy consuming).

Kations	Intra [mM]	Extra [mM]
K^+	124	2
Na^+	10	125
Ca^{2+}	5	2
Mg^{2+}	14	1
Kations total	153	130

Anions	Intra [mM]	Extra [mM]
Cl^-	2	77
HCO_3^-	12	27
other	139	26
Anions total	153	130

2.5.1 Membrane potential, membrane capacitance, membrane resistance

Membrane potential

The *membrane potential* is defined as the potential jump between the extra- and intracellular space. The extracellular space is set to zero by convention.
Th membrane potential is spatially variable. Therefore, cells are not isopotential. Ion flux propagates along the membrane potential gradient.

Theorem 1. *Let I_L define the* axial ion flux*, R_L the* axial resistance*, and r_L the intracellular resistance of a cylinder with length L and cross-section area. Let V_1 be the potential at $x = 0$ and V_2 the potential at $x = 2$. Assuming ohmic flux, this yields:*

$$I_L = \frac{V_2 - V_1}{R_L} \tag{2.1}$$

$$R_L = r_L \frac{L}{\pi a^2} \tag{2.2}$$

Electrotonic properties of a cell are governed by its geometry.
Q: How does a local change in the membrane potential affect cell A and B?

A: Morphologically compact cells are *electrotonically compact*. Therefore, cell B will be close to isopotential.
⇒ Simplest cell model: Interpret the cell as a single unit.

Membrane capacitance

The bi-lipid plasma membrane can be interpreted as a capacitor.

Theorem 2. *Let C_m be the* membrane capacitance*, Q the* charge difference*, and V_m the* membrane potential*. Then*

$$Q = C_m V_m \tag{2.3}$$