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**NEURAL DYNAMICS OF ADULT-BORN DENTATE GYRUS
GRANULE CELLS IN A HIPPOCAMPAL MICROCIRCUIT WITH
MULTI-COMPARTMENTAL CONDUCTANCE-BASED NEURONS**

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ÇOK-BÖLMELİ KONDÜKTANS-TEMELLİ NÖRONLARLA
KURULMUŞ BİR HIPOKAMPAL MIKRODEVREDE YETİŞKİN-
KÖKENLİ DENTAT GİRÜS GRANÜL HÜCRELERİNİN
NÖRONAL DİNAMİKLERİ

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ÖZET

ÇOK BÖLMELİ İLETKENLİK TABANLI NÖRONLARLA KURULMUŞ BİR HİPOKAMPAL MİKRODEVREDE YETİŞKİN KÖKENLİ DENTAT GIRÜS GRANÜL HÜCRELERİNİN SİNİRSEL DİNAMİKLERİ

Hipokampus, uzun süreli hafıza oluşumu, depolanması ve konsolidasyonunun yanı sıra uzamsal yönelim ve navigasyon için de oldukça önemlidir. Hipokampus üç farklı katmandan oluşur: Dentat Girus (DG), Cornu Ammonis (CA) ve Subikulum. DG, hipokampal işlev, örüntü ayrımı ve hafıza kodlamasında önemli bir rol oynar. Yetişkin-kökenli granül hücreleri (YK-GH) biyofiziksel ve işlevsel özelliklerini entegre ederek devrelere katkıda bulunur. Bu YK-GH'ler olgun GH'lere kıyasla önemli elektrofizyolojik farklılıklar gösterir: Yüksek uyarılabilirlik ve seyrek aktivite gösterirler. Bu tez, YK-GH'lerin farklı morfolojik özelliklerinin nöral yanıt özelliklerini nasıl etkilediğini araştırmaktadır. Çok-bölmeli kondüktans-temelli model, parametre seçimi sırasında toplanan bilgiler kullanılarak Python ortamında Brian2 modülü üzerinde tasarlanmıştır. Sonuçlarımıza göre, YK-GH'lerde morfoloji, hala gelişmekte olmalarına rağmen, olgun GH'lere kıyasla daha hızlı aksiyon potansiyeli kinetiği için optimize edilmiştir ve uyarılabilirlikteki farklılıklar, DG işlevinde, özellikle de örüntü ayrımı ve nöral plastisite gibi süreçlerde farklı rollere katkıda bulunabilir.

Anahtar Kelimeler: Yetişkin-Kökenli Granül Hücreleri, Olgun Granül Hücreleri, Hesaplamalı Granül Hücre Modelleri, Morfoloji, Sinirsel Dinamikler

ABSTRACT

NEURAL DYNAMICS OF ADULT-BORN DENTATE GYRUS GRANULE CELLS IN A HIPPOCAMPAL MICROCIRCUIT WITH MULTI-COMPARTMENTAL CONDUCTANCE-BASED NEURONS

The hippocampus is crucial in long-term memory formation, storage, and consolidation, as well as spatial orientation and navigation. Three distinct layers constitute the hippocampus: the Dentate Gyrus (DG), Cornu Ammonis (CA), and Subiculum. The DG plays an important role in hippocampal function, pattern separation, and memory encoding. Adult-born granule cells (AdB GCs) contribute to circuits by integrating their biophysical and functional properties. These AdB GCs display important electrophysiological differences compared to the mature GCs: They are highly excitable and show sparse activity. This thesis investigates how the distinct morphological features of adult-born granule cells impact neural response characteristics. The multi-compartmental conductance-based model is designed on Python environment with Brian2 module, using the information gathered during literature survey. Based on the results, the morphology of AdB GCs are optimized for faster action potential kinetics compared to mature GCs even though they are still developing and The differences in excitability could contribute to distinct roles in DG function, particularly in processes such as pattern separation and neural plasticity.

Keywords: Adult-Born Granule Cells, Mature Granule Cells, Computational Models of Granule Cells, Morphology, Neural Dynamics

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To the memory of Kubilay SERT, whose inspiration continues to guide me.

DECLARATION FORM

I hereby declare that all the information and documents in this study have been obtained in accordance with academic principles, that all visual, auditory, and written data and results have been presented in compliance with scientific ethical standards, that no alterations have been made to the data used, that all sources have been cited in accordance with scientific norms, and that, except where references are provided, this thesis is original, produced by myself, and written in accordance with the Uskudar University Institute of Health Sciences Thesis Writing Guide.

Date

14.02.2025

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TABLE OF CONTENTS

	<u>Page</u>
ÖZET	i
ABSTRACT.....	ii
ACKNOWLEDGEMENTS	iii
DECLARATION FORM	iv
TABLE OF CONTENTS	v
LIST OF TABLES	vii
FIGURES.....	viii
SYMBOLS AND ABBREVIATIONS.....	ix
1. INTRODUCTION	1
1.1. Hypothesis	1
1.2. Objectives	2
2. LITERATURE SURVEY.....	4
2.1. Hippocampal Anatomy	4
2.2. Dentate Gyrus and Granule Cells	6
2.2.1. Dentate Gyrus Cytoarchitecture.....	6
2.2.2. Granule Cell Morphology and Biophysical Characteristics	10
2.2. Adult Hippocampal Neurogenesis	12
2.2.1. Immature neurons	14
2.3. Computational Models of Granule Cells	15
3. METHODS	19
3.1. Model Topology	19
3.2. Conductance-based Model Biophysics	22
3.3. Current Injection	23
3.4. Simulation Design.....	24

3.3.1. Brian2.....	24
3.4. Model Response Analysis.....	25
3.4.1. Action Potential Waveform Characteristics	25
3.4.2. Action Potential Propagation	25
3.4.3 Frequency-Current Plots	25
3.4.4 Dynamic Response Modulation.....	25
4. RESULTS	27
4.1. Action Potential Waveform Characteristics	27
4.2. Frequency-Current Relationship.....	29
4.3. Action Potential Propagation	30
4.4. Dynamic Gain Analysis	35
5. DISCUSSION	37
6. CONCLUSIONS AND SUGGESTIONS.....	39
REFERENCES.....	40
Appendix 2. Curriculum Vitae.....	50

LIST OF TABLES

Table 1: Overview of the main kinds of models used to study the morphological and physiological alterations of the dentate gyrus granule cells.	17
Table 2: Geometrical Properties of Mature Granule Cell.....	20
Table 3: Geometrical Properties of Young Adult - Born Granule Cell.	20
Table 4: Electrophysiological properties of mature and adult-born granule cells.	28
Table 5: Frequency-Current Plot Curve Fitting Parameters.	29
Table 6: The velocity of dendritic (v_d) and axonal (v_a) propagation for mature and AdB GCs	31



FIGURES

Figure 1: The anatomy of human hippocampus and entorhinal cortex.	4
Figure 2: Entorhinal cortex-hippocampus excitatory microcircuit.....	5
Figure 3 Summary of IN subtypes in the DG.	6
Figure 4: The Anatomy of the Subgranular Zone of Dentate Gyrus	8
Figure 5: The structural organization and connectivity of granule cells in the dentate gyrus of the hippocampus.	11
Figure 6: Morphological maturation of AdB.....	14
Figure 7: The topology of mature and young adult-born granule cells.	21
Figure 8: Membrane potential dynamics of mature and young adult-born granule Cells.	28
Figure 9: Firing frequency of GCs changes according to varying input currents.....	30
Figure 10: Distance-dependent (x,t) delay in action potential propagation for mature and adult-born granule cells.	32
Figure 11: Delay–dependent distance (t,x) in action potential propagation for mature and adult-born granule cells.	33
Figure 12: V_{peak} -dependent (t-x) distance in action potential propagation for mature and adult-born granule cells.	34
Figure 13: The attenuation of action potential amplitude.....	34
Figure 14: Dynamic Gain analysis plot.	36

SYMBOLS AND ABBREVIATIONS

AdB	Adult-Born
AIS	Axon Initial Segment
AP	Action Potential
CA	Cornu Ammonis
CA1	Cornu Ammonis Area 1
CA2	Cornu Ammonis Area 2
CA3	Cornu Ammonis Area 3
CA4	Cornu Ammonis Area 4
C_m	Specific Membrane Capacitance
DG	Dentate Gyrus
EC	Entorhinal Cortex
EChip	Entorhinal cortex - hippocampus circuit
E_l	Leak Reversal Potential
f-I	Frequency - current
GC	Granule Cell
GL	Granule cell layer
HH	Hodgkin-Huxley Model
HIPP	Hilar Perforant path-associated cells
IFWd ²	Inverse full width at half maximum method
IHWd ²	Inverse half width at half maximum method

L	Section Length
LM	Lamina Moleculare
LPP	Lateral Perforant Pathway
ML	Molecular layer
MPP	Medial Perforant Pathway
MTL	Medial Temporal Lobe
NR	Node of Ranvier
PSTH	Peristimulus time histogram
PVBC	Parvalbumin-positive basket cells
R_i	Cytoplasmic Resistance
SAS	Santhakumar, Aradi, and Soltesz's model
SGZ	Subgranular zone
SST+	Somatostatin-positive interneurons
T2N	TREES-to-NEURON model

1. INTRODUCTION

The hippocampus, the key brain region of medial temporal lobe (MTL), was first described by Julius Caesar Arantius. A pioneering anatomist and surgeon of the 16th century, he coined the term *hippocampus*, due to its seahorse-like shape (hippos [‘horse’] and kampos [‘sea monster’] in Greek). At that time, various terms for this region were also suggested by different scientists, such as ‘*white silkworm*’, ‘*horn of Ammon*’, and ‘*Ram’s horn*’. However, the term hippocampus has become the most commonly used term in the literature (Bir et al., 2014).

The hippocampus is primarily associated with memory and is a complex brain structure located deep in the MTL. In all mammals, the hippocampal region has the densely packed cell layers of the hippocampus proper and Dentate Gyrus (DG), which at most septotemporal levels appear to fit together like interlocking arcs. DG has three main layers: The molecular layer (ML), the Granule cell layer (GL) and the hilus. In addition to the three main layers, there is a thin layer called subgranular zone (SGZ) between the GL and hilus. DG receives signals via projections from Entorhinal Cortex (EC) and the signals from perforant pathway goes to CA3 via the axons of GC (Amaral et al., 2007). Granule Cells (GCs) are the main cells of the DG and one of the few cell types that undergo neurogenesis in the adult brain. GCs play a significant role in memory, learning, and diseases like epilepsy because of their high rate of neurogenesis. (Tejada et al., 2014). The structure and function of adult-born (AdB) and mature GCs differ in many ways. AdB GC maturation is characterized by the expression of specific molecular markers as well as distinct morphological features. (Llorens-Martín et al., 2016). These differences between AdB and mature GCs allow them to make different contributions to neural networks.

1.1. Hypothesis

The central question of the thesis is *how the distinct morphological features of AdB GCs impact the neural response characteristics*. This question can be addressed with a simplistic design of multi-compartmental conductance-based neurons, that have modified Hodgkin-Huxley (HH) type Na^+ , K^+ and leak conductances.

This thesis addresses the main questions by investigating how the distinct morphological features of AdB GCs affect

- the action potential waveform characteristics,
- action potential back- and forward-propagation,
- firing rate response to increased stimulus strength,
- modulation firing rate response to fluctuating noisy stimulus.

1.2. Objectives

Our understanding of the hippocampus requires enhancement through models that adequately consider its distinct morphological and biophysical attributes. The ultimate goal of this thesis is *the construction and response analysis of multi-compartmental conductance-based models of mature and AdB GCs and integration into an entorhinal cortex-hippocampus microcircuit with glutamatergic feedforward and feedback connections.*

In order to achieve this goal, the stages of the thesis with respective objectives are as follows:

- **Parameter Selection:** This stage includes the construction of a library of morphological and biophysical parameters through an intensive survey of existing experimental literature. The objective is to construct the model cell using thorough analyses of real DG granule cells. We use the Hodgkin-Huxley model, which incorporates K^+ and Na^+ channels, to determine biophysical properties. The biophysical parameters had to be simplified compared to actual cells to study the direct effects of morphologies.
- **Model Construction:** In this stage, the multi-compartmental conductance-based model is designed on Brian2, using the information gathered on Parameter Selection. Brian2 has a significant advantage in using differential equations to describe continuous dynamics and update statements for discrete events instead of relying on predefined "black-box" models, and this leads to excellent code readability and adaptability since every aspect of the model can be explicitly defined in a single Python script, with the model's equations stated in mathematical notation and only a tiny amount of Brian-specific vocabulary used (Stimberg et al., 2019).

- **Action Potential Waveform and Propagation:** Following this, we analyze action potential (AP) waveforms under constant current injection to evaluate various electrophysiological properties, such as single AP characteristics, phase plots, AP width, onset slope, threshold, and the minimum current (I_{min}) needed to generate an AP. We determined the minimum current by applying current at the center of the soma and gradually increasing its amplitude until we elicited the first spike. We also examine propagation plots and conduction velocity to assess the dynamics of AP propagation across the cellular compartments.
- **Firing Rate Response:** Linear responses were evaluated using frequency-current ($f-I$) curves generated from step and ramp current injections. The current injection/simulation design used either stepwise or ramp increases in current to find out how input current and output firing frequency are related.
- **Dynamic Response:** Dynamic responses were assessed through raster plots, peristimulus time histograms, and gain plots obtained under noisy sinusoidal current injection and analyzed through raster plots, peristimulus time histograms (PSTH), ensemble averages, and fitting procedures. We also calculated the gain and cutoff frequency to characterize the system's response to these inputs.
- **Model Validation :** Finally, we compared the models and findings from existing literature to validate their accuracy and relevance.

2. LITERATURE SURVEY

2.1. Hippocampal Anatomy

The hippocampus is crucial in long-term memory formation, storage, and consolidation, as well as in spatial orientation, and spatial navigation (Squire et al., 2004). One key function is the capacity to quickly encode distinct representations of similar inputs and later retrieve them when provided with incomplete or noisy cues. These processes are theoretically described as pattern separation and pattern completion, respectively (Marr, 1971; Treves and Rolls, 1994; Yassa and Stark, 2011; Santoro, 2013; Chavlis et al., 2017). The hippocampus needs to receive sensory information from the cerebral cortex to maintain these functions.

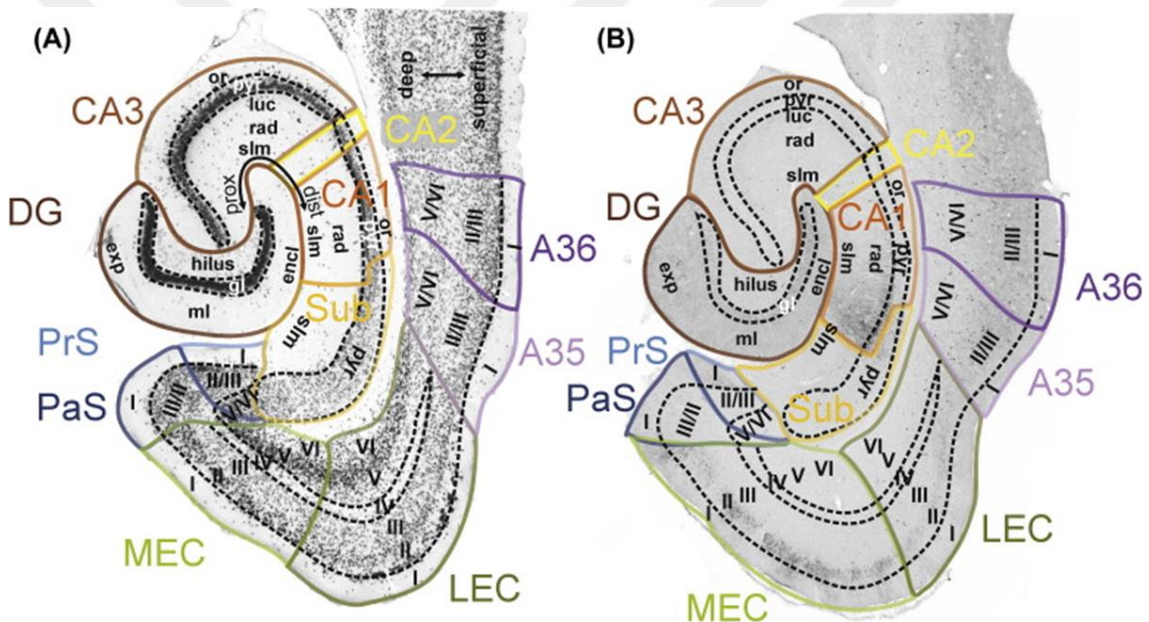


Figure 1: The anatomy of human hippocampus and entorhinal cortex.

The NeuN-stained (A) and calbindin-stained (B) human hippocampal sections. The figure is adapted from Cappaert et al. (2015). DG; dark brown, CA3; medium brown, CA2; yellow, CA1; orange and the subiculum (Sub; yellow), the presubiculum (PrS; medium blue), parasubiculum (PaS; dark blue), lateral entorhinal cortex (LEC; dark green), medial entorhinal cortex (MEC; light green) and perirhinal cortex areas 35 (A35; pink) and area 36 (A36; purple). The cortical layers (Roman numerals) and the transverse proximodistal axis as well as the superficial to deep or radial axis are marked. dist, distal; encl, enclosed blade of the DG; exp, exposed blade of the DG; luc, stratum lucidum; or, stratum oriens; prox, proximal; pyr, pyramidal cell layer; rad, stratum radiatum; slm, stratum lacunosum-moleculare.

The hippocampus consists of two different layers (Figure 1), the DG and Cornu Ammonis (CA). The CA is divided into four subregions known as CA1, CA2, CA3, and

CA4. One of the most important morphological distinction among CA regions and DG is the type of primary excitatory neuron : Pyramidal neuron somata form the *stratum pyramidale* of CA, whereas granule cell somata form the *stratum granulare* of DG (Graves et al., 2013)

Multimodal sensory data processed by the EC can enter the hippocampus via two different pathways: the **monosynaptic** or **temporoammonic direct pathway** from the EC to CA1 and the **trisynaptic loop (EChip)** (Remondes & Schuman, 2003). The EChip is illustrated in Figure 2, which shows the key pathways within the hippocampal circuitry, also highlighting its connections with cortical inputs and outputs. The EChip begins with projections from layer II neurons of the EC to DG via the **perforant pathway (PP)**. GCs in the DG relay signal to the CA3 through the **mossy fibers**, which is essential for relaying sensory information and initiating the hippocampal response. As the next step, CA3 projects to the CA1 pyramidal neurons via the **Schaffer collaterals**. The **monosynaptic pathway** is shown in Figure 2 as projections from layer III of the entorhinal cortex to CA1 pyramidal neurons, bypassing the DG and CA3 regions and providing a direct route for input to CA1 (Kajiwara et al., 2008).

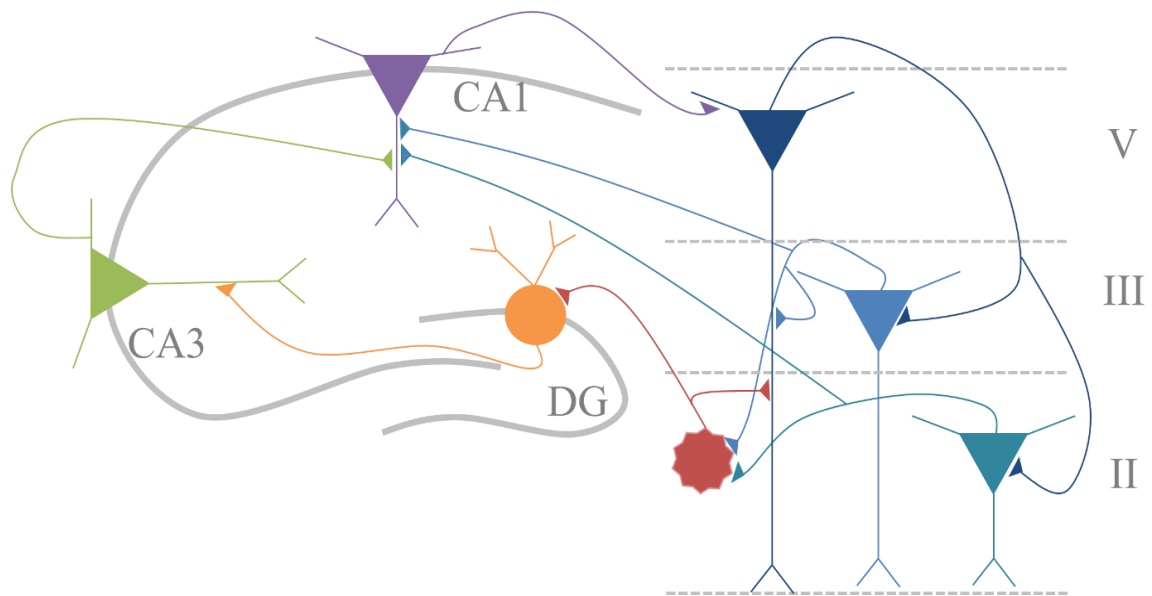


Figure 2: Entorhinal cortex-hippocampus excitatory microcircuit.

The figure represents the detailed cytoarchitectural organization of hippocampus and entorhinal cortex, together with the excitatory connections within EChip. The microcircuit structure highlights the complex connectivity through pathways that are essential for the transfer and processing of sensory and cognitive information, contributing to memory formation and retrieval. The large triangles represent pyramidal neuron somata (Purple, Green, Dark blue, Blue, Turquoise). Small triangles represent excitatory synapses. Orange: Granule neuron. Red: EC2 stellate cell.

2.2. Dentate Gyrus and Granule Cells

2.2.1. Dentate Gyrus Cytoarchitecture

In all mammals, the hippocampal region contains densely packed cell layers of hippocampus proper and DG, many of which appear to fit together like interlocking arcs at the septotemporal level (Manns & Eichenbaum, 2007). DG forms a C-shaped structure that is separated ventrally from the CA1 and the subiculum by the fused hippocampal fissure (Figure 1 & 2) (Amaral et al., 2007). The **parvalbumin-positive basket cells (PVBC)** and **somatostatin-positive (SST+) interneurons** are two important inhibitory neuron types (Figure 3) in DG due to their reciprocal connections with GCs (Lee et al., 2015). PVBCs are found in **granule cell layer (GL)** and SST+ are in **molecular layer (ML)** of DG. Through their inhibitory feedback, they aid to maintain a balance between excitation and inhibition within the DG and are crucial for learning, memory, and neural plasticity.

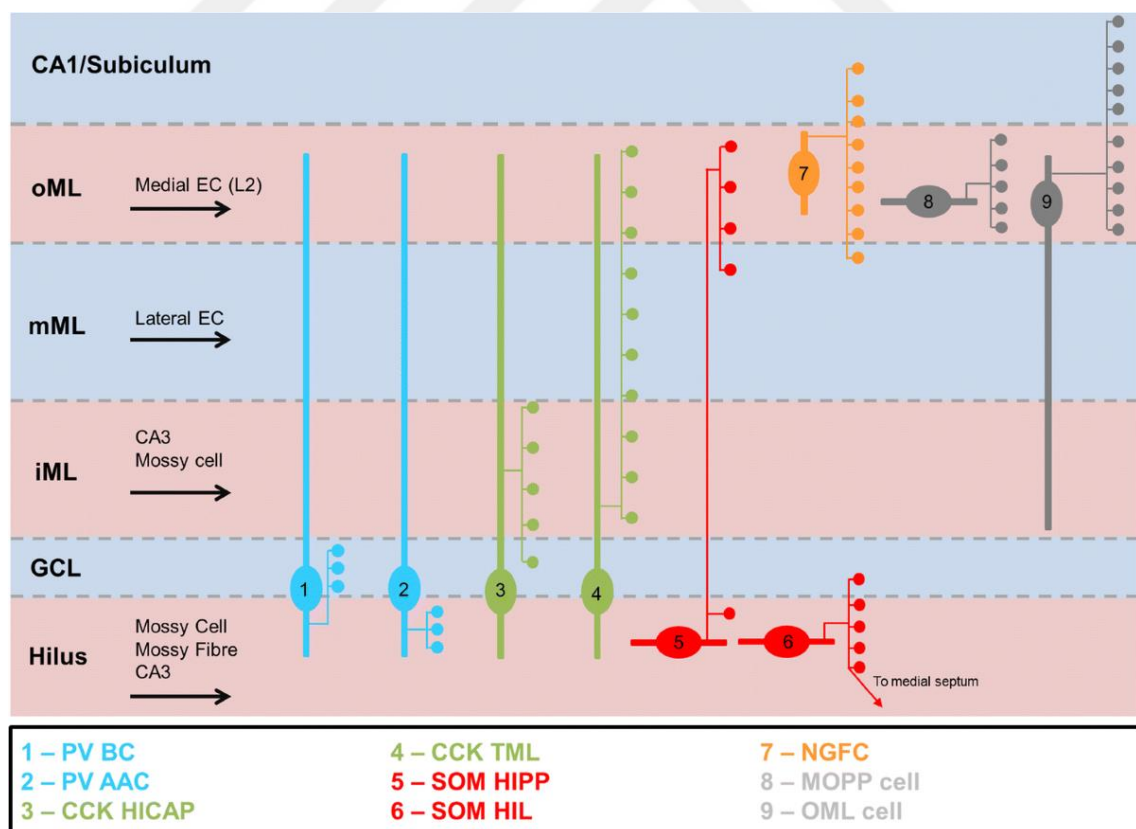


Figure 3 Summary of IN subtypes in the DG.

Dendrites (thick lines), axon distribution (thin lines) with major terminal fields (circles), DG layers (dashed lines). Granule cell layer (GCL); Inner molecular layer (Iml); Medial molecular layer (Mml); Outer molecular layer (oML) and hippocampal fissure (thick dashed line) (Booker and Vida, 2018).

2.2.1.1. Layers of Dentate Gyrus

DG has unique cytoarchitecture with a highly organized neuronal arrangement and lamination. There are three main layers: the ML, the GL and the hilus (polymorphic layer).

1. **The molecular layer (ML)** is the outermost layer composed of dendritic arbors from granule cells and axonal projections of PP (Schultz & Engelhardt, 2014). It contains sparse inhibitory interneurons (Figure 3) that modulate GC activity, such as
 - *Molecular Layer Perforant Path-Associated (MOPP) Interneurons* that receives input from EC via perforant path and provide feedback inhibition on GC,
 - *Neurogliaform Cells* that they provide inhibition by targeting dendrites of GCs, and
 - *Hilar Interneurons* that make projection into the ML layer to inhibit GC dendrites.

These inhibitory interneurons all together shape the firing patterns of GCs and maintain the excitatory-inhibitory balance (Chauhan et al., 2021). This system ensures that GCs can detect, distinguish, process and send important data faster, which aids in DG functioning in detection, separation, encoding, and storage of patterns.

2. **The granule layer (GL)** is the main cell layer of the DG, where the GC somata are located. This layer is the primary site for excitatory input processing and the dominant cell type is the GC. The GL acts as gatekeeper for hippocampal circuits due to its functional and cytological organization (Insausti & Amaral, 2004). GCs are the primary excitatory neurons of the DG and have small, round somata. They receive excitatory input from the EC (i.e. layer 2 stellate cells (L2S)) on their dendrites in ML, and project their axons (*mossy fibers*) to pyramidal cells of CA3 (Amaral et al., 2007) passing through *hilus*. The human GL contains approximately 9×10^6 GC somata (Seress et al., 1988). GL filter and processes information being transmitted on ECHip before it is propagated to CA regions, which is crucial for pattern separation (Figure 3).

3. **The hilus (or polymorphic layer)** is located beneath the GL and contains diverse neuronal populations. *Mossy cell* of the hilus is an excitatory interneuron that provides feedback excitation to GCs and inputs to the contralateral DG (Insausti & Amaral, 2004). The hilus is also populated by inhibitory interneurons (Figure 3), such as chandelier cells, mossy cells, and SST+ interneurons that regulate the activity of GCs and mossy cells. *Chandelier Cells* (rare, but present in DG) target the AIS of GCs and exert inhibitory control over their output (Kung et al., 2022). The cell bodies of hilar interneurons also reside in hilus (Booker and Vida, 2018). This layer plays a significant role in modulating DG output and ensuring stability within the EChip circuit (Seress et al., 1988).

In addition to the three main layers, the thin layer between the GL and the hilus, **the subgranular zone (SGZ)** (Figure 4), has a unique role in DG function. SGZ remains as one the few active neurogenic niches in the adult mammalian brain, where neural progenitor cells (NPC) differentiate into immature AdB GCs. Hippocampal adult neurogenesis (HANG) is a crucial source of plasticity and learning (Catavero et al., 2018). Costa et al. (2015) suggest that HANG is modulated by physiological stimuli and cognitive and emotional states. Moreover, they also stated that multiple pharmacological interventions targeting cognition modulate HANG.

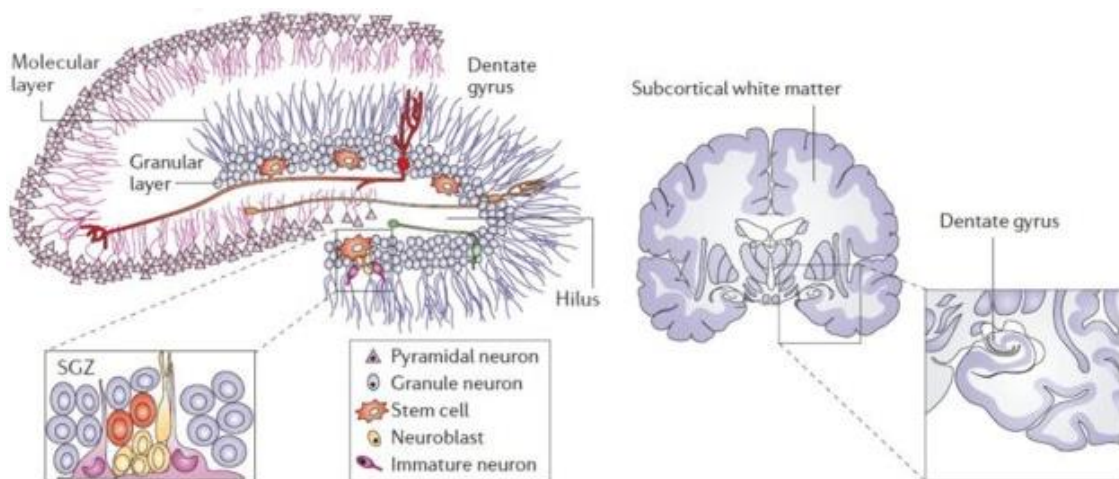


Figure 4: The Anatomy of the Subgranular Zone of Dentate Gyrus (Chalard , 2019).

2.2.1.2 Dentate Gyrus Connectivity

The earliest hippocampal models (Marr, 1971) did not clearly consider the role of DG in separation, instead they predicted that the recurrent axons within CA3 would be ideal for forming memory representations. The DG performs pattern separation of cortical inputs before sending its differentiated outputs to CA3 according to theoretical models. (McNaughton et al., 1990; Treves et al., 2008; Rolls et al., 2010). Indeed, DG receives signals via PP, and send signals to CA3 via the axons of GCs, and this shows that DG is ideally located to do this (Amaral et al., 2007). The DG pattern separation process is vital for distinguishing between similar inputs and allows the brain to form unique representations of comparable yet distinct experiences. This process is supported by robust inhibitory control from interneurons and achieved via selective activation of GCs.

The first information for the communication between DG and hippocampus comes from EC and it is carried from EC to DG via PP. Network modulation between the EC and the DG through the PP involves dynamic adjustments to synaptic strength and neural activity patterns, ensuring efficient information processing (Seo et al., 2022). The *medial perforant pathway (MPP)* transports ipsilateral inputs, whereas the *lateral perforant pathway (LPP)* transports contralateral signals from EC L2S (Toader et al., 2013). With the process of receiving and processing inputs from the EC, the DG acts as the gateway to the hippocampal circuitry and controls that the information is appropriately filtered and organized before further processing in downstream regions as CA3 and CA1. HANG further supports this function of DG because AδB GCs are highly plastic and contribute to encoding novel information while integrating it into existing memory circuits (Toda et al., 2019).

Modulation of DG activity occurs via synaptic plasticity, neuromodulators (e.g., dopamine, acetylcholine), and inhibitory interneurons that regulate excitation and prevent overactivation. These processes enable the DG to filter and transform inputs, facilitating functions such as pattern separation and memory encoding in the hippocampal network (Szabo et al., 2017). *Memory interference* is crucial for accurately recalling specific events, and DG prevents memory interference by transforming highly similar input patterns into distinct output signals (Schmidt et al., 2012). Additionally, DG is important for behaviorally discriminating similar spatial memories, predicting that

DG place cells change their relative spatial tuning for memory formation. Due to these functions, DG is crucial for encoding new episodic and spatial memories.

2.2.2. Granule Cell Morphology and Biophysical Characteristics

The elliptical cell body of the GC is around 10-18 μm and the apical dendrites of GC extend into the ML, where they make synapses with the axon terminals of EC neurons on the PP (Amaral et al., 2007). The spines of the GC dendrites are shaped by the learning and memory processes that alter size, shape, density and formation through long-term potentiation (LTP) and long-term depression (LTD), depending on the nature and frequency of synaptic activity (Zhou et al., 2004).

The GC morphology (i.e., dendritic and axonal branching patterns) (Figure 5) and its wide range of connections (e.g., mossy fibers projecting to the CA3 region) allow them to filter PP inputs arriving in the ML and send signals to the CA3 selectively. Here, they play a key role in pattern separation, which ensures similar input patterns are stored as distinct representations in the hippocampus (Yassa & Stark, 2011). The unmyelinated axons of GC with dense collaterals form the mossy fibers that project to the apical dendrites of CA3 pyramidal neurons.

AdB GCs have initial electrophysiological characteristics different from mature GCs. They have a higher input resistance (R_{in}), lower voltage thresholds, and slower membrane time constants. They are also more prone to LTP (Esp3sito et al., 2005; Laplagne et al., 2006). R_{in} for mature GCs are around 100-300 $\text{M}\Omega$, where it can be as high as 4 $\text{G}\Omega$ for AdB GCs (Heigele et al., 2016). GCs have reduced ion channels that open at resting potential, such as inward-rectifier potassium channels (K_{ir}). The kinetics of K_{ir} , as well as dendritic and axonal processes, increase the input resistance of immature neurons up to 1 $\text{G}\Omega$ (Liu et al., 1996; Mongiat et al., 2009; Schmidt-Hieber et al., 2004). Another distinctive feature of AdB GCs is the short-term expression of T-type calcium channels, which underlies the sudden voltage spike caused by low-threshold calcium induced by physiological conditions (Goncalves et al., 2016). However, mature GCs are unable to produce calcium-induced voltage spikes to low threshold and no significant sodium-induced voltage spikes are seen when pharmacologically blocking T-type channels (Schmidt-Hieber et al., 2004; Martinello et al., 2015). Action potentials initiated by sodium currents trigger short-term calcium currents with a high amplitude in both

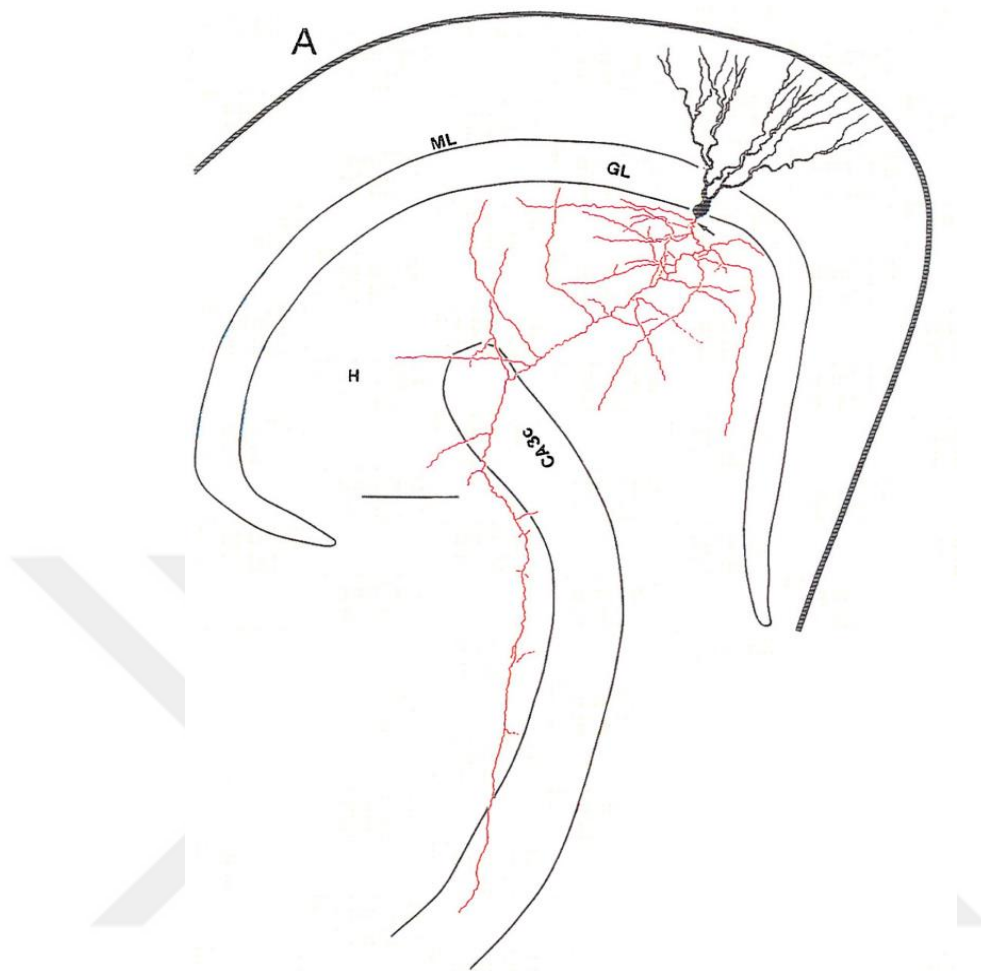


Figure 5: The structural organization and connectivity of granule cells in the dentate gyrus of the hippocampus. (Wheeler et al., 2024)

mature and AdB GCs (Stocca et al., 2008). However, AdB GCs can perform temporal summation of inputs more efficiently than mature GCs because they show longer-lasting temporal wave spikes in their proximal and distal dendrites (Stocca et al., 2008). Differences in calcium currents may also result from synaptic plasticity. Dendrites of mature GCs are generally described as passive integrators that strongly dampen voltage signals (Krueppel et al., 2011). As a consequence, the amplitude of the backpropagating action potential is attenuated throughout the dendrites of mature GCs, and excitatory postsynaptic potentials (EPSPs) show a steep decline from the dendrites to the soma.

Cell excitability studies on DG GCs show that these cells show a resistance to fire synchronously during network bursts. This is due to intrinsic biophysical properties, but

is considered to be a consequence of feedforward and feedback GABAergic inhibition, which is a feature of DG circuit function (Coulter et al., 2007).

DG GCs have lower excitability than other hippocampal cells. This low excitability of GCs is due to the degree and nature of GABAergic inhibition. GCs express a complex and varying set of GABA(A) receptor subunits (Heinemann et al., 1992). Due to this receptor diversity, GCs have both synaptic and extrasynaptic GABA(A) receptors. Extrasynaptic GABA(A) receptors in GCs are particularly non-desensitized and have a high affinity for GABA. This results in the activation of a tonic current by ambient GABA levels in the extracellular space. This tonic current contributes significantly to the circuit properties of the DG (Yeung et al., 2003). In animal models of temporal lobe epilepsy, both synaptic and extrasynaptic GABA(A) receptors show profound dysregulation, which may contribute to the characteristic hippocampal hyper-excitability in this disorder (Lothman et al., 1992).

2.2. Adult Hippocampal Neurogenesis

Joseph Altman and his colleagues first described adult neurogenesis in the rodent brain in 1965 and in hippocampus in 1975 (Altman, 1965, REF). HANG is a form of structural plasticity in the brain, in which new neurons are generated from adult NPCs. The generation of new GCs from adult NPCs is a highly dynamic process, and, at the same time, it is tightly regulated at multiple developmental stages, which include the proliferation and differentiation of NPCs, migration of differentiating neuroblasts from SGZ to GL, survival of immature GCs in GL and their integration into pre-existing hippocampal networks in parallel to maturation processes (Costa et al., 2015).

The generation of AdB GCs in the adult brain of vertebrates occurs only in SGZ (Kempermann et al., 1998; Llorens-Martín et al., 2016). The major pool of NPCs is composed of radial glia-like **Type I** cells, that have a single apical prolongation that enters the GL, branching sparsely in the ML (Kempermann et al., 2004). Type I cells divide either symmetrically to generate Type I cells or asymmetrically, resulting in one **Transiently Amplifying Cell (TAC, Type II)**. Type II cells are intermediate neuronal precursors, that quickly divide and differentiate, or die (Homem et al., 2015). The greatest morphological and electrophysical changes occurs during the cellular processes of the last NPC type, **the neuroblasts (Type III cells)**. In these cells, the expression of

immature neuronal markers, such as doublecortin (DCX) progressively increases. Neuroblasts migrate vertically into GL using Type I apical extensions and terminate differentiation on neural lineage (Wu et al., 2024). Cells at the end of this stage, the immature AdB GCs, are vertically oriented, with a rounded or slightly triangular nucleus and a visible apical dendrite (Kempermann et al., 2004; Llorens-Martín et al., 2016).

Zhao et al. (2006) Retroviral labeling of newborn AdB GCs highlighted that their apical dendrites reached the ML and the edge of the ML on 10 and 21 days after their birth. The dendritic tree of AdB GCs becomes increasingly complex as they mature. After dendritic spines form, the number of branches, volume, and complexity of the dendritic tree gradually increase until reaching a plateau at 8-10 weeks (van Praag et al., 2002). When completely mature, AdB GCs are integrated into the local circuitry and become biophysically and morphologically identical to embryonic-born mature GC (Zhao et al., 2006; Llorens-Martín et al., 2015; Llorens-Martín et al., 2016).

The maturation stages of AdB GCs can be identified with unique morphological features rather than only by the expression of specific molecular markers; see Figure 2-A (Llorens-Martín et al., 2016). Mature GCs typically have only one primary apical dendrite that is oriented vertically toward the ML. The reason for the wide branching pattern of this dendrite is to receive PP axons, known as the main afferent. Additionally, cells with multiple primary apical dendrites are mainly located in the outer GL and represent mature GCs rather than AdB GCs (Redila and Christie, 2006). The morphological properties during the stages of GC development are shown in figure 6.

HANG gives rise to only one type of neuron: the GCs of DG. There are unconfirmed claims in the literature, but there is no decisive evidence that other neuronal cell types can be generated under physiological conditions (Kempermann et al., 2015). Approximately 700 new neurons are integrated in DG per day in adult humans, which corresponds to an annual turnover rate of 1.75% of the renewing population of DG GCs (Spalding et al. 2013). The presence of new hippocampal GCs in humans, as well as their dynamic regulation under physiological conditions, suggest that adult neurogenesis may be an important aspect of brain function.

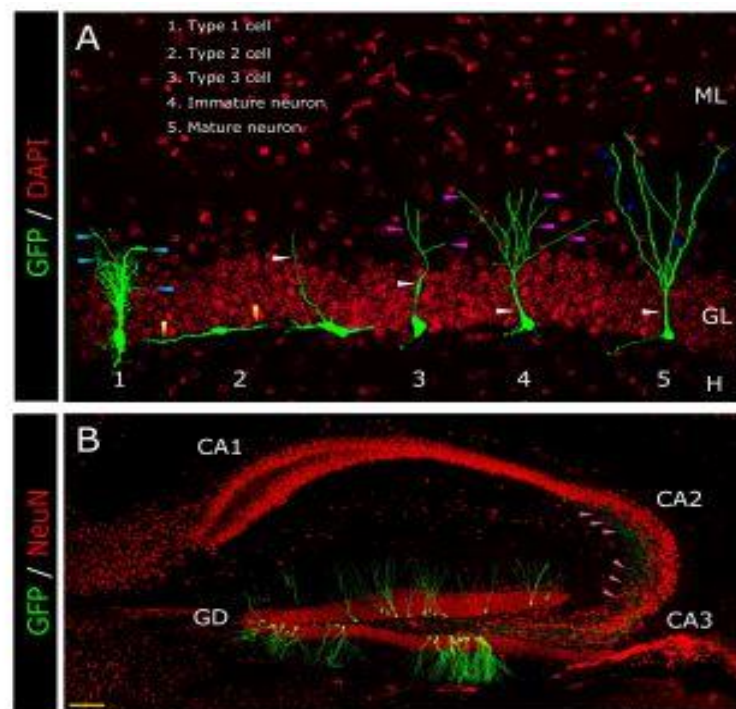


Figure 6: Morphological maturation of AdB.

A) Newborn neurons progress through distinct stages. Type-1 cells have a single apical process branching sparsely in the molecular layer and divide asymmetrically into progenitors. Type-2 cells develop short tangential processes and dense nuclei, while Type-3 neuroblasts undergo major changes, gaining vertical orientation, rounded nuclei, and an apical dendrite. Immature neurons then refine their dendritic trees to resemble mature granule cells. (B) Axons of AdB grow and project toward the CA3 and CA2 regions (Llorens-Martín et al., 2016)

There is evidence that HANG is functionally relevant to hippocampus-dependent cognitive activity and state, and in disorders associated with anxiety, depression and cognitive impairment (Costa et al., 2015). Many factors that modulate cognition also modulate hippocampal neurogenesis. These include pharmacological modulation of inherent intracellular intrinsic pathways of plasticity, as well as modulation by physiological stimuli such as running and interactions with enriched environments. In addition, cognitive processes associated with the hippocampus are improved by specifically increasing the number of newborn neurons in the DG (Costa et al., 2015).

The firing activity of AdB GCs before and after spatial learning indicates that they are actively integrated into circuits during specific spatial learning tasks (Temprana et al., 2015). Compared to mature GCs, AdB GCs formed at a specific developmental stage were found to be more activated when re-exposed to the same spatial learning task. That is, these cells become more sensitive to previous learning experience. (Tashiro et al., 2017). These findings highlights that AdB GCs are preferentially recruited over mature

GCs to generate specific memory circuits (Ramirez-Amaya et al. 2006; Kee et al. 2007; Tashiro et al. 2007).

Thus, sustained neurogenesis in the adult hippocampus and ongoing maturation of AdB GCs allow the DG network to regulate both stable analysis of "old" features and adaptation to new settings, enabling precise and distinct representations of new memories across the lifespan (Costa et al., 2015).

2.2.1. Immature neurons

The structure and function of young AdB GCs are different from mature GCs in a large number of ways, with the synaptic connectivity, membrane excitability, and firing patterns (Nakashiba et al., 2012). Biophysically, mature GCs have a high input resistance, low resting membrane potentials, and higher spike-frequency adaptation (Brunner et al., 2014). Mature GC's firing rate decreases over time in response to a constant stimulus. This is due to their mature intrinsic properties, such as stronger potassium channel activation that reduces their excitability (Pardi et al., 2015).

The maturational stages that AdB GCs go through before becoming fully mature can be identified on the basis of unique morphological features (Matin et al., 2016). The morphological analyses indicate that structural maturation of developing AdB GCs is completed by 3 weeks after cell birth (Beining et al., 2017). The AdB GCs have short and less complex dendritic branching and sparse dendritic spines, but mature GCs have well-developed and extensive dendritic branches and dense dendritic spines. Mature GCs have larger somata and this reflects their fully developed state (Amaral et al. 2007). Moreover, while mature GCs have fully established axonal projections to CA3, AdB GC's axonal projections are still developing (Martin et al., 2016). Mature GCs primarily contribute to the maintenance of established neural circuits due to their more stable synaptic connectivity but the AdB GCs exhibits increased synaptic plasticity (Caroni et al., 2012). The functional differences of AdB GCs, such as excitability and increased plasticity make them critical for adaptive learning processes (Temprana et al., 2015). While mature GCs have lower input resistance (R_{in}), AdB GCs have higher R_{in} due to smaller dendritic processes and fewer synaptic connections. Therefore, they are more excitable and can generate larger voltage changes with smaller inputs (Stone et al., 2011). A small soma and less extensive dendritic branching cause lower capacitance, faster signal propagation, and response times in AdB GCs while mature GCs have higher

capacitance, slower membrane time constants, and signal integration (Brunner et al., 2014).

2.3. Computational Models of Granule Cells

The aim of computational models of neuronal function is to “*explain how electrical and chemical signals are used in the brain to represent and process information*” (Sejnowski, 1988). An overview of computational models on DG GCs are provided in Table 1.

Conductance-based models for single neuron voltage dynamics and neural network models have proven essential in clarifying the role of the DG in hippocampal activities such as pattern separation and circuit plasticity (Hendrickson et al., 2011). Santhakumar, Aradi, and Soltesz (SAS) (2005) developed the first conductance-based DG network model to investigate the effects of epilepsy-induced changes on DG activity. The scaled-down model of the dentate gyrus (DG) operates at a scale of 2000:1 and features simplified compartmental representations of granule cells (GCs), mossy cells, basket cells, and hilar perforant path-associated (HIPPA) cells. These four-dendrite models are based on morphological and biophysical parameters derived from existing literature. Active conductances are uniformly distributed across all compartments, with the exception of sodium and fast delayed potassium conductances. This model incorporates only AMPA receptors and fast GABAergic synapses, having been modified from previous conductance-based granule cell models (Aradi & Holmes, 1999; Tejada & Roque, 2014). The SAS model suggests that the morphological differences of AdB and mature GCs contribute to processes like pattern separation in terms of differences in dendrites and excitability. Furthermore, another study (Singh et al., 2023) focusing on the biophysical properties of GCs using a modified SAS model suggest that GCs have intrinsic cellular mechanisms that enable frequency-dependent pattern separation, which is consistent with the “U” shaped input frequency-pattern separation relationship observed at the network level. The researchers hypothesized that the intrinsic capacity of GCs may contribute to the role of the hippocampus in efficient and interference-resistant memory storage.

Table 1: Overview of the main kinds of models used to study the morphological and physiological alterations of the dentate gyrus granule cells.

Reference	Description	Purpose	URL
<i>Aradi & Holmes, 1999</i>	A DG GC model that includes nine different channel types according to the HH formalism with their respective channel kinetics.	Contribution of each channel type to spiking behavior with a focus on the mechanisms underlying post spike events.	https://pubmed.ncbi.nlm.nih.gov/10406134/
<i>Santhakumar et al., 2005</i>	Biophysically realistic and anatomically representative computational DG model.	SAS model is developed to independently examine whether it is the loss of mossy cells or the sprouting of mossy fibers that leads to dentate hyperexcitability.	https://pubmed.ncbi.nlm.nih.gov/15342722/
<i>Schmidt-Hieber et al., 2007</i>	Combined dual whole-cell patch-clamp recording with high-resolution two-photon microscopy to investigate detailed passive cable models of hippocampal GCs from adult mice. Highlights the biophysical properties of dendrites.	How dendrites of GC process synaptic inputs and how GCs detect and respond to coincident synaptic inputs.	https://pubmed.ncbi.nlm.nih.gov/17670990/
<i>Ferrante et al., 2009</i>	Biophysically and anatomically realistic computational models of feed-forward inhibition in DG based on compartmental models of GC and MOPP interneuron.	How feed-forward inhibition regulates neuronal responses.	https://pubmed.ncbi.nlm.nih.gov/19815518/
<i>Tejada et al., 2014</i>	Focuses on dendritic remodeling and spine loss. It uses reconstructed GCs to study changes in neuronal morphology and their impact on network dynamics.	To investigate how morphological changes in GCs caused by epilepsy affect DG hyperexcitability and contribute to epileptogenesis.	https://pubmed.ncbi.nlm.nih.gov/24811867/
<i>Beining et al., 2017</i>	The T2N model implements known differences in ion channel composition/ morphology and reproduces data from mouse or rat, mature or adult-born GCs, as well as pharmacological interventions and epileptic conditions.	T2N model is developed to simulate the electrical and biophysical properties of DG GCs.	https://pubmed.ncbi.nlm.nih.gov/29165247/
<i>Chavlis et al., 2017</i>	Four types of DG neuron models with no internal geometry. Dendritic pruning and growth approaches were used to investigate whether the number of GC dendrites affects pattern separation.	Role of DG GC dendrites in pattern separation.	https://pmc.ncbi.nlm.nih.gov/articles/PMC5217096/

Another recent extensive model is TREES-to-NEURON (T2N) which is an interface linking compartmental modeling environment NEURON with morphology modeling and analysis tools of Matlab and TREES toolbox (Beining et al., 2017). T2N allows fast and simple incorporation of diverse morphologies in compartmental simulations, facilitating the search for morphologically detailed biophysical models. It provides a strong framework for studying the roles of mature and AdB GCs in neural processing. This framework extends the HH formalism by incorporating HH-like equations for ion channel dynamics into a more complicated and realistic neural framework. The HH model is ideal for simplicity and foundational understanding, yet T2N was created for purposes, such as translating biological complexity into computational models.

In this thesis, I utilized multi-compartmental modelling with a reduced topology (i.e. on dendritic and axonal branching patterns), that still reflect the most distinctive morphological features and differences of AdB and mature GCs. Utilizing a simplistic HH model, only with Na^+ and K^+ currents, and keeping the active biophysical parameters constant for both cell types allowed us to emphasize the contribution of morphological properties rather than biophysical ones.

3. METHODS

In this chapter, I will introduce the steps I followed to set up and test the model. The first section explains the morphological construction of mature and immature AdB GCs, including model topologies and morphological parameters for each compartment. The second section describes the biophysical model, including the equations for membrane current, ion channel gating kinetics and synaptic current, and passive and active biophysical parameters. The third section explains the simulation design and the details of the simulation platform. Lastly, the fourth section describes the protocols for tests conducted on the models and the parameters measured by each test.

3.1. Model Topology

The model topology and morphological parameters are determined by a comparative analysis of existing experimental and computational studies (Chavlis et al., 2017). The most striking morphological difference between mature GCs and AdB GCs is the length and branching of the axon (Zhao et al., 2006). For dendritic branching, we adapted the 3-dendrite model of Chavlis et al. (2017), with shortened segment length in AdB GCs.

The general topology of the mature and AdB GC models are given in Figure 7 and the morphological parameters for each compartment are given in Table 2 for mature GCs and Table 3 for AdB GCs (Claiborne et al., 1990; Schmidt-Hieber et al., 2007; Beining et al., 2017; Chavlis et al., 2017). **Apical Stem** is the initial compartment before the first apical dendrite branching. **Proximal 1** is the first compartment of proximal apical dendrite before further branching (only on right main branch). **Proximal 2** is the first proximal apical compartment after the final apical branching. **Lamina Moleculare (LM)** describes the branches at the end of the distal apical dendrite compartment. In **axon terminal**, the initial diameter is 1 μm , and the final diameter is 2 μm .

Table 2: Geometrical Properties of Mature Granule Cell.

<i>Compartments</i>	<i>L(μm)</i>	<i>Diam (μm)</i>
<i>Soma</i>	12	12
<i>Stem</i>	1	3
<i>Proximal 1</i>	20	0.95
<i>Proximal 2</i>	55	0.95
<i>Medial</i>	75	0.90
<i>Distal</i>	75	0.80
<i>Lamina Molecularis</i>	50	0.80
<i>Axon Hillock</i>	10	1.5
<i>Axon Initial Segment</i>	40	1.3
<i>Axonal Segment</i>	100	1
<i>Axon Terminal</i>	4	1 -> 2

Table 3: Geometrical Properties of Young Adult - Born Granule Cell.

<i>Compartments</i>	<i>L(μm)</i>	<i>Diam (μm)</i>
<i>Soma</i>	10	10
<i>Stem</i>	1	3
<i>Proximal 1</i>	20	1
<i>Proximal 2</i>	25	0.95
<i>Medial</i>	45	0.90
<i>Distal</i>	45	0.80
<i>Lamina Molecularis</i>	25	0.80
<i>Axon Hillock</i>	10	1.5
<i>Axon Initial Segment</i>	40	1.3
<i>Axonal Segment</i>	100	1
<i>Axon Terminal</i>	4	1 -> 2

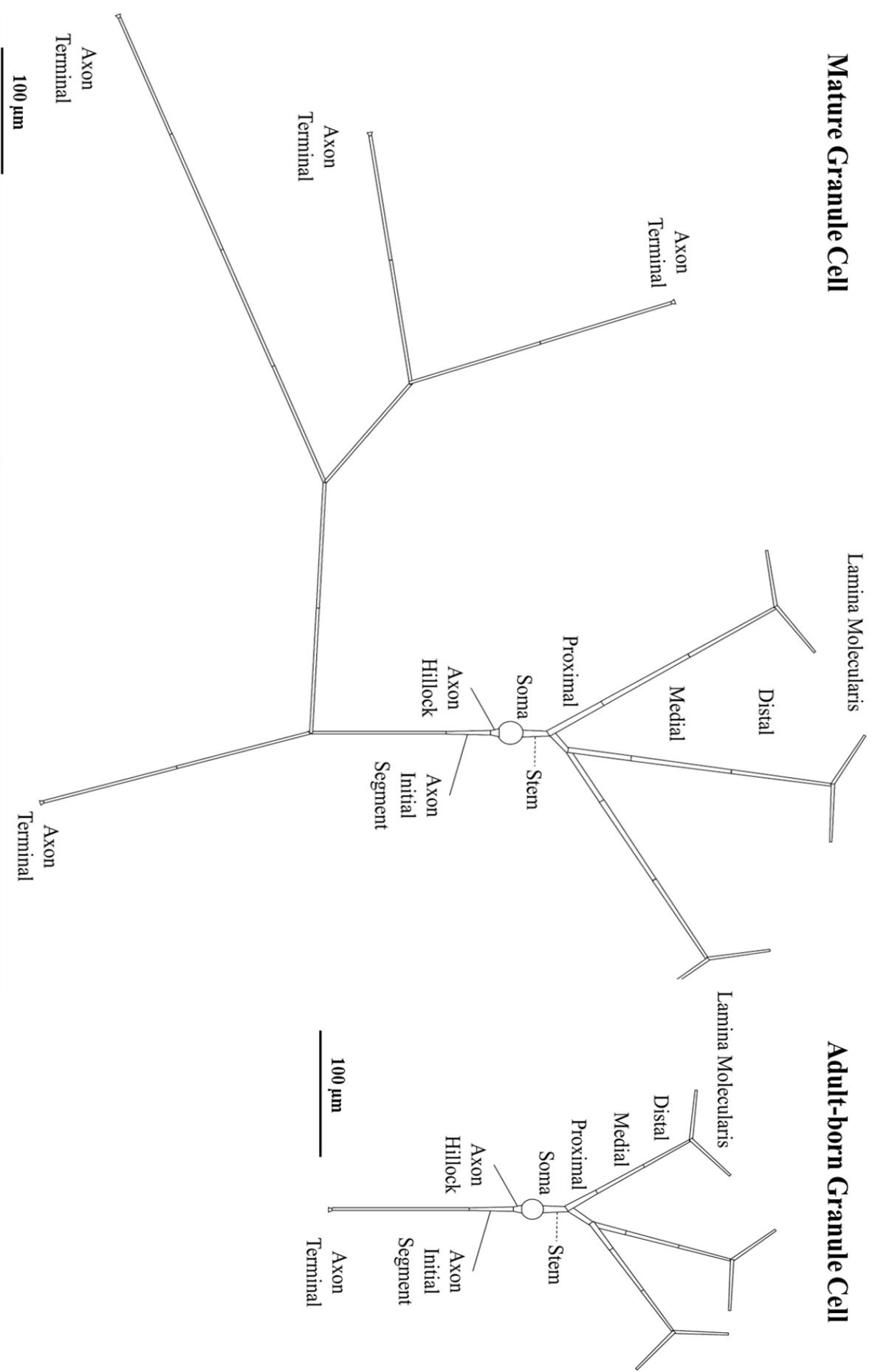


Figure 7: The topology of mature and young adult-born granule cells.

3.2. Conductance-based Model Biophysics

Hodgkin and Huxley published a series of papers in the Journal of Physiology in 1952 and they made the first mechanistic explanation of the action potential. The conductance-based model in this thesis utilized a modified HH-type ion channel gating kinetics.

The conductance-based model was designed as

$$C_m \frac{dv}{dt} = -I_m - I_{syn} + I_{inj}$$

where C_m is $0.88 \mu\text{F}/\text{cm}^2$ for AdB GC and $1 \mu\text{F}/\text{cm}^2$ for mature GC. The membrane current, I_m , consisted of HH-type conductances Na^+ , K^+ and leak conductances as

$$I_m = \bar{g}_L(v - E_L) + \bar{g}_{Na}m^3h(v - E_{Na}) + \bar{g}_Kn^4(v - E_K)$$

where $\bar{g}_L = 3 \times 10^{-4} \text{ S}/\text{cm}^2$, $\bar{g}_K = 0.036 \text{ S}/\text{cm}^2$, $E_L = -76.5 \text{ mV}$, $E_{Na} = 50 \text{ mV}$ and $E_K = -90 \text{ mV}$. The density distribution of Na_v channels are reflected on $\bar{g}_{Na}$ as $0.05 \text{ S}/\text{cm}^2$ for soma, $0.5 \text{ S}/\text{cm}^2$ for AIS and NR and $0.005 \text{ S}/\text{cm}^2$ for dendrites.

The gating kinetics for any voltage-gated channel was defined as the activation and inactivation rates of channel subunits as

$$\frac{dz}{dt} = \frac{z_\infty - z}{\tau_z}$$

$$z_\infty = \frac{\alpha_z}{\alpha_z + \beta_z}$$

$$\tau_z = \frac{1}{\alpha_z + \beta_z}$$

where z is a generalized gating particle. The gating kinetics for Na_v was defined over the activation (**m**) and inactivation (**h**) functions, whereas K_v was defined with a singular activation (**n**) function as follows (Aradi and Holmes, 1999) :

$$\alpha_m = \frac{0.32(13 - v_T)}{e^{\frac{13-v_T}{4}} - 1}$$

$$\beta_m = \frac{0.28(v_T - 40)}{e^{\frac{v_T-40}{5}} - 1}$$

$$\alpha_h = 0.128 e^{\frac{17-v_T}{18}}$$

$$\beta_h = \frac{4}{1 + e^{\frac{40-v_T}{5}}}$$

$$\alpha_n = \frac{0.032(15 - v_T)}{e^{\frac{15-v_T}{5}} - 1}$$

$$\beta_n = 0.5e^{\frac{10-v_T}{40}}$$

3.3. Current Injection

In order to mimic the subthreshold activity driven by baseline ionic current load at a given time, a sustained constant current ($I_{inj} = \mu_I$) was placed at the soma for each cell. The characteristics of action potential waveform from soma and axon initial segment (AIS) with the input current $I_{inj} = I_{min}$. These characteristics were defined over threshold potential (V_{thr}), onset rapidness (ρ), peak potential (V_{peak}) and action potential width ($\Delta t_{1/2}$). Firing rate responses and frequency-current plots were also obtained under constant current, increased with repeated test with a current increment Δ_I for $T = 200$ ms for each step.

In the brain, neurons receive information under excitatory and inhibitory synaptic inputs. The activity of numerous synapses in the cortex creates a noisy background for the information processing of a single neuron. Noisy background can be characterized by Gaussian statistics and an autocorrelation function exponentially decaying with the time constant τ_I . The noisy current implemented in dynamic response analysis was generated by an Ornstein-Uhlenbeck stochastic process with zero mean and variance σ_I^2 to mimic the synaptic noisy input,

$$\frac{dI_n}{dt} = -\frac{I_n}{\tau_I} + \sqrt{\frac{2\sigma_I^2}{\tau_I}} \xi_t$$

where ξ_t is a random variable drawn at every time step from a Gaussian distribution with a zero mean. The phase-locking capacity of the model is analyzed by the addition of sinusoidal current with a frequency of f_I on the noisy current and the mean constant current as

$$I_{inj} = I_n + \mu_I + \sin(2f_I\pi t)$$

The constant current amplitude (μ_I) remained below minimum spike-triggering threshold (μ_{min}).

3.4. Simulation Design

The model construction and simulations were performed in Python environment with Brian2 module (Stimberg et al., 2019). The analyses were performed with user-defined functions in Python, partially utilizing Brian2. Experiments were run with $\Delta_t = 0.01$ ms and the implicit backward Euler integration. The voltage traces are recorded from the midpoint of every compartment. The details for experimental protocols are detailed in respective sections.

3.3.1. Brian2

The model was created by utilizing the Brian2 simulation platform. The module has a significant advantage in using differential equations to describe continuous dynamics and update statements for discrete events instead of relying on predefined "black-box" models. This leads to excellent code readability and adaptability since every aspect of the model can be explicitly defined in a single Python script, with the model equations stated in mathematical notation and only a small amount of Brian-specific vocabulary used (Stimberg et al., 2019). Because the model is explicitly described, all features are documented and can be found in the primary simulation description file, which eliminates the need for the previously relied upon "black-box" models, as mentioned in studies (Brette, 2012; Stimberg et al., 2014).

In this thesis, each cell was designed and compiled using *SpatialNeuron* class in Brian2. For building neurons, the *exponential Euler* method was implemented.

3.4. Model Response Analysis

3.4.1. Action Potential Waveform Characteristics

We defined the action potential waveform characteristics of each cell over the threshold potential (V_{thr}), onset rapidness (ρ), peak potential (V_{peak}) and width ($\Delta t_{1/2}$). V_{thr} was measured as the voltage at the time where dV/dt reaches and exceeds 10 V/s (Naundorf et al., 2006). Action potential half amplitude ($V_{1/2}$) was measured as the half of difference between the V_{peak} and V_{thr} , and $\Delta t_{1/2}$ was estimated as the full width of action potential at $V_{1/2}$. The two methods used to measure ρ were the inverse full width at half maximum (IFWd²) and the inverse half width at half maximum (IHWd²) of d^2V/dt^2 peak as described by Aldohbeyb et al. (2021).

3.4.2. Action Potential Propagation

The delay of action potential propagation from AIS to other compartments (Δt_d) was measured as $\Delta t_d = t_{1/2,i} - t_{1/2,AIS}$ where $V_m(t_{1/2,i}) = V_{1/2}$ at compartment “i”. The attenuation of action potential amplitude was recorded by the attenuation of V_{peak} ($\Delta V_{peak,i}$) at compartment “i” as $\Delta V_{peak,i} = V_{peak,AIS} - V_{peak,i}$. Both Δt_d and $\Delta V_{peak,i}$ were plotted over the distance to the center of AIS from the center of respective compartments. The velocity of dendritic (v_d) and axonal (v_a) propagation was estimated by fitting ($x, \Delta t_d$) plot with a linear function, $x = v t + a$, where a is a constant.

3.4.3 Frequency-Current Plots

The frequency – current plots were obtained by injecting a step-wise increasing constant current for 500 ms intervals, starting with $\mu_I < \mu_{min}$ and increasing with the increment $\Delta\mu$. The firing frequency was estimated over the somatic voltage traces.

3.4.4 Dynamic Response Modulation

Dynamic response of the model is analyzed as the phase-locking capacity to a noisy sinusoidal input current with varying of f_I . The explored range of f_I was 1-500 Hz, however, both models displayed very low gain after 150 Hz. Therefore, the gain plots were shown only for $f_I < 150$ Hz. The noisy current parameters were not varied. The spikes were pooled according to spike times and binned into a peristimulus time

histogram (PSTH), with bin sizes determined by the value of f_I . The average spike count over 1000 repetitions were fitted using a least-squares method with the equation.

$$v_t = v_0 + v_1 \sin(2\pi f_I t + \phi)$$

Gain of the modulation was obtained as v_1/v_0 for frequency f_I . v_0 was chosen as ≈ 10 Hz. The confidence interval for $\alpha = 0.05$ was given as error bars on f_I vs v_1/v_0 plot.



4. RESULTS

4.1. Action Potential Waveform Characteristics

The action potentials (APs) from soma and AIS of mature and AdB GCs were recorded under constant current injection at the soma (I_{inj}) that resulted in 10 Hz firing rate. The changes in V_{peak} , V_{thr} , $\Delta t_{1/2}$ and onset rapidness according to two different methods (IFWd² and IHWd²) for AdB and mature GCs are given in Table 4.

The somatic voltage traces in Figure 8- A illustrates that the V_{peak} is 34.5 mV for mature GCs and 34.7 mV for AdB GCs, which is slightly higher than mature GCs. For AIS, V_{peak} for mature GCs is 46.1 mV and 47.6 mV for AdB. This indicates that strong depolarization occurs at AIS for both groups, with a slightly higher maximum potential in AdB GCs. V_{thr} is approximately -37.4 mV for mature GC and approximately -39.8 mV for AdB GC both in soma and AIS. This suggests that mature GC requires greater subthreshold depolarization to reach the threshold and AdB GC is more easily excited.

The timing of AP is also slightly different, with mature GCs initiating slightly later than AdB. Moreover, the $V_{1/2}$ is -2.5 mV for AdB GC and -1.4 mV for mature GC, which implies that AdB GC might have a faster depolarization phase. The $\Delta t_{1/2}$ values for both models are similar at the soma and AIS.

For the onset rapidness, the IFWd2 method yielded a notable difference between AdB (20 ms⁻¹) and mature GCs (12.5 ms⁻¹). These results indicate that AdB GC AP onsets are steeper than mature GC at soma. Therefore, we concluded that the IFWd2 method provides more meaningful results than the IHWd2 method about the onset rapidness of these cells. When we look at the phase plots in figure 8, the mature and AdB GC both had similar phase plots. The slight difference in soma is at the onset depolarization phase (steeper) and maximum dv/dt in AIS.

Table 4: Electrophysiological properties of mature and adult-born granule cells.

	SOMA						AIS					
	V_{peak} (mV)	V_{thr} (mV)	$V_{1/2}$ (mV)	$\Delta t_{1/2}$ (ms)	ρ_{IFWd2} (ms ⁻¹)	ρ_{IHWd2} (ms ⁻¹)	V_{peak} (mV)	V_{thr} (mV)	$V_{1/2}$ (mV)	$\Delta t_{1/2}$ (ms)	ρ_{IFWd2} (ms ⁻¹)	ρ_{IHWd2} (ms ⁻¹)
Mature GC	34.5	-37.4	-1.4	0.46	12.5	33.3	46.1	-37.4	4.3	0.66	25	50
AdB GC	34.7	-39.8	-2.5	0.48	20	33.3	47.6	-39.8	3.9	0.66	25	33.3

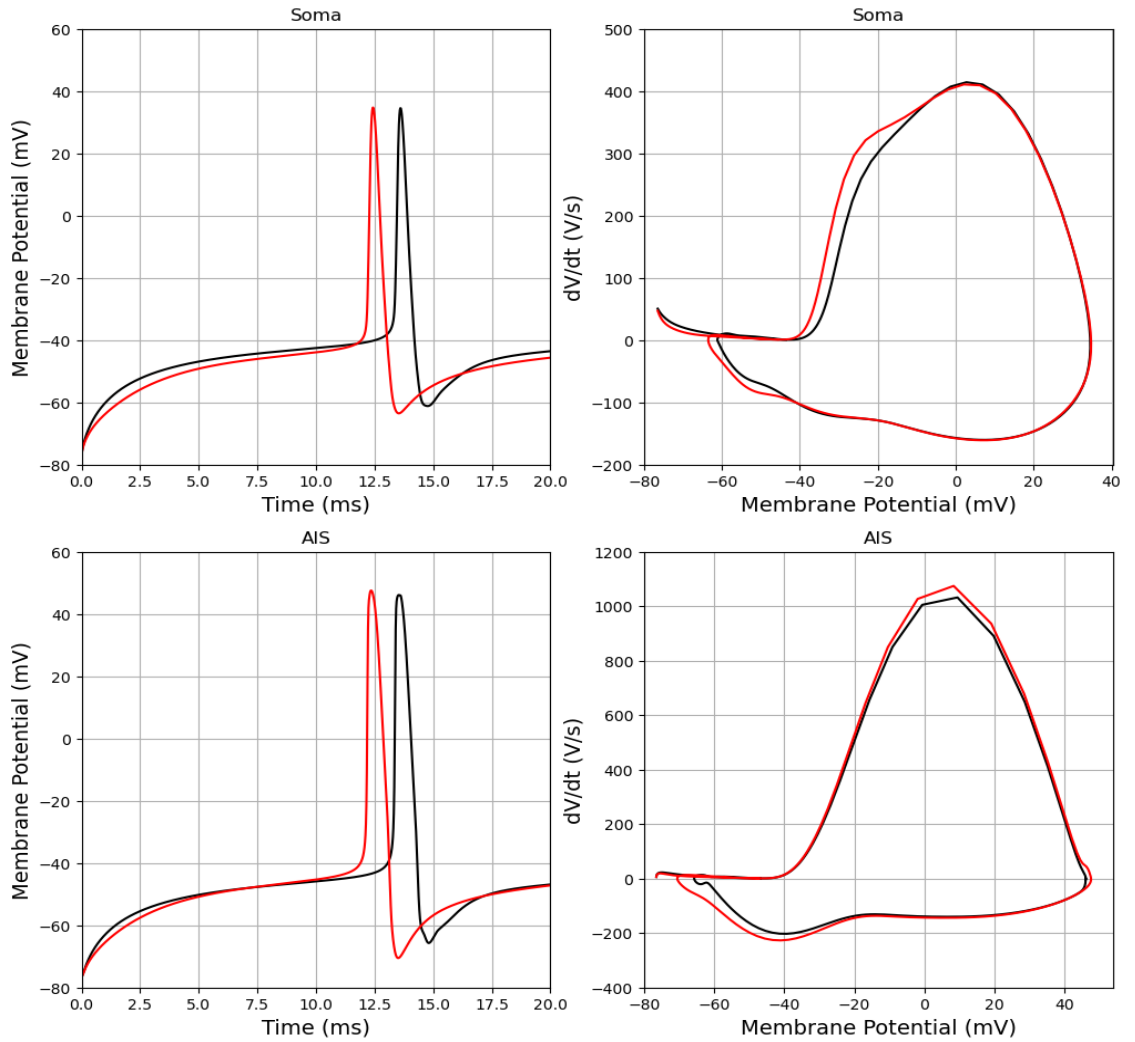


Figure 8: Membrane potential dynamics of mature and young adult-born granule Cells.

Red: Young adult-born granule cells and black: Mature granule cells.

4.2. Frequency-Current Relationship

The F-I curve shows how the firing frequency (Hz) of GCs changes according to varying input currents. The plot in Figure 9 exhibits a non-linear increase in frequency as the amplitude of the current injection increases. At low input current increments, the increase in firing rate grows relatively fast, while at higher input current increments the increase becomes slower approaching a saturation.

The firing rate (f) in response to current (I) injection were fit with the function

$$f = f_h * \ln(I) + f_{limit}$$

using least square method with Levenberg-Marquadt algorithm. The variables and root mean square deviation (RMSD) for mature and AdB GCs are given in Table 5.

Table 5: Frequency-Current Plot Curve Fitting Parameters.

f_h : inflection frequency, f_{limit} : Limiting saturation frequency. RMSD : Root mean square deviation for least square method.

	f_h	f_{limit}	RMSD
<i>Mature GC</i>	105.2	462.45	0.9923
<i>AdB GC</i>	83.714	424.27	0.9781

AdB GC and mature GCs show a similar curve, but f - I curves differ slightly in saturation and inflection frequency (Figure 9). The frequency of AdB is slightly lower than mature GCs at lower currents. This indicates that AdB requires more current to achieve a similar firing rate with mature GCs. However, the firing frequencies converge, showing that the two cell types exhibit similar maximal firing capacities at higher currents. As the curve fitting suggests (Table 5), both cell types seem to approach saturation point at frequencies of approximately 400 Hz; though there is a slight difference between the GCs. We can understand from the convergence at higher currents that AdB can achieve firing rates comparable to mature GCs under strong stimulation, reflecting their potential to integrate effectively into the neural network.

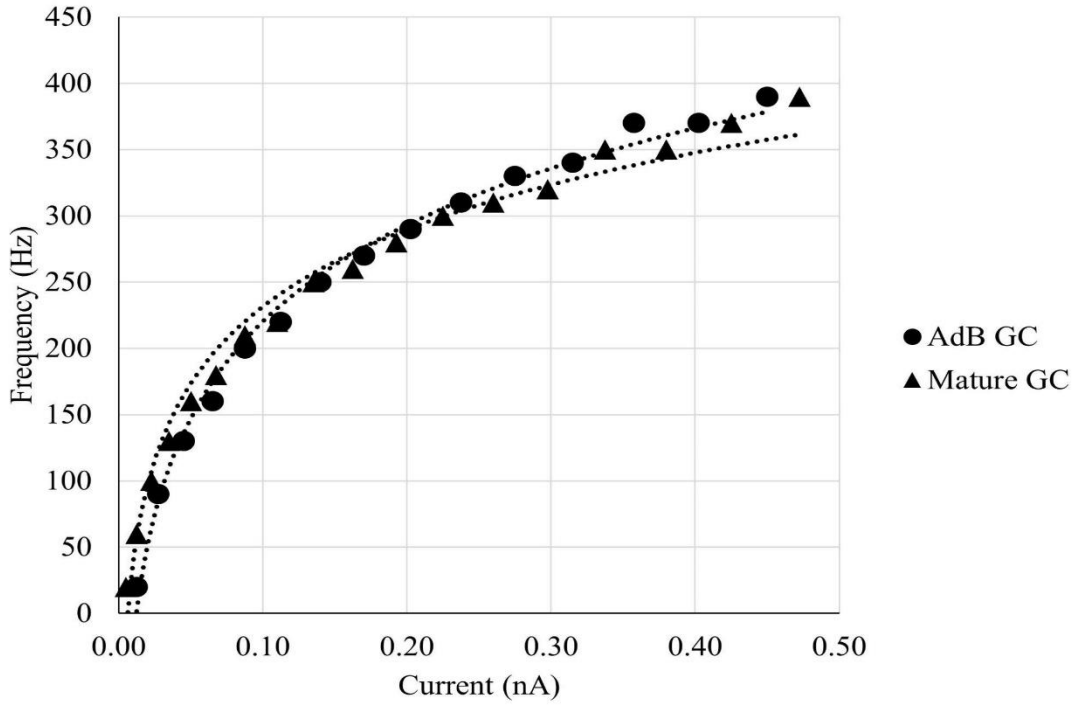


Figure 9: Firing frequency of GCs changes according to varying input currents.

4.3. Action Potential Propagation

Action potential propagation provides insight in the timescale of signal transduction. The Δt_d and $V_{peak,I}$ of APs across dendritic and axonal compartments was analyzed to investigate the AP propagation dynamics. Linear regression was performed to calculate the v_d and v_a AP propagation. These analyses reflect the efficiency of signal transmission in GCs.

The delay of AP propagation from AIS to other compartments was measured as :

$$\Delta t_d = t_{1/2,i} - t_{1/2,AIS}$$

where $V_m(t_{1/2,i}) = V_{1/2,i}$ at the midpoint of the AP in compartment “i”.

The somatic backpropagation delay was 70 μs for both models. Mature and AdB GCs show increased delay with increasing distance from AIS (Figure 10 A-B). The t-x graph (Figure11) shows that AdB GC exhibits lower slopes for dendritic and axonal propagation compared to mature GC. The v_d and v_a propagation was estimated by fitting $(x, \Delta t_d)$ plot with a linear function, $x = v t + a$, where a is a constant. The v_d and v_a are

given in Table 6 for mature and AdB GC. These results indicate that AdB GCs transmit signals faster than mature GCs.

The attenuation of action potential amplitude was recorded by the attenuation of V_{peak} ($\Delta V_{peak,i}$) at compartment “i” as $\Delta V_{peak,i} = V_{peak,AIS} - V_{peak,i}$. Both Δt_d and $\Delta V_{peak,i}$ were plotted over the distance to the center of AIS from the center of respective compartments. Both GCs exhibit a decrease in dendritic V_{peak} as distance increases (Figure 12) but there is no significant difference between both models (Figure 13). This result shows that AdB GC display similar performance in dendritic backpropagation in terms of signal integrity and propagation efficiency.

Both GCs showed an increasing delay with greater distance to AIS. At higher distances, mature GCs exhibit slightly higher delay. The data for both cells indicate similar attenuation patterns. These similarities indicate similar integrative properties in signal transmission.

Table 6: The velocity of dendritic (v_d) and axonal (v_a) propagation for mature and AdB GCs

	v_d ($\mu\text{m/ms}$)	v_a ($\mu\text{m/ms}$)
<i>Mature GC</i>	560.21	337.57
<i>AdB GC</i>	523.69	1045.1

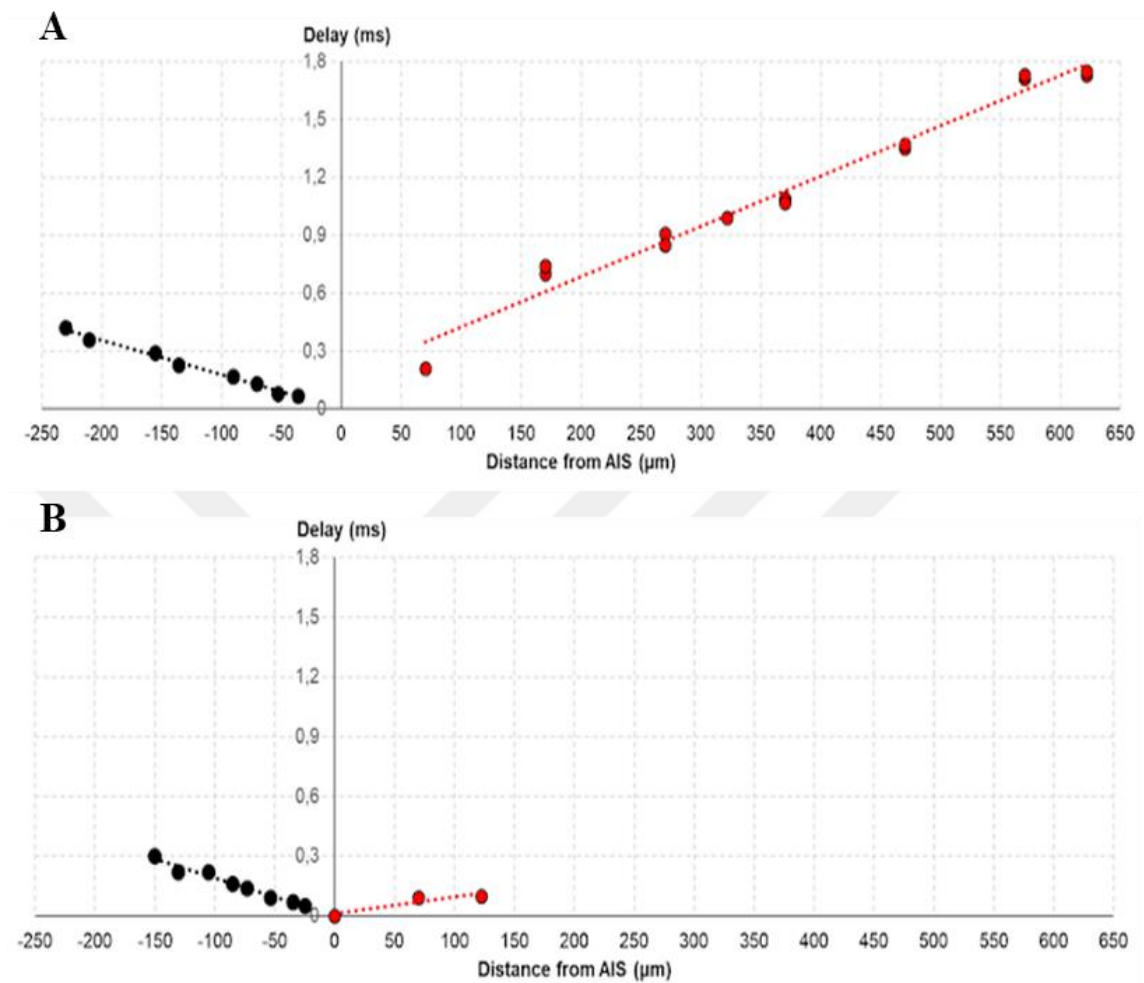


Figure 10: Distance-dependent (x,t) delay in action potential propagation for mature and adult-born granule cells.

The dendritic and axonal action potential propagation for (A) mature GCs and (B) young adult-born GCs.

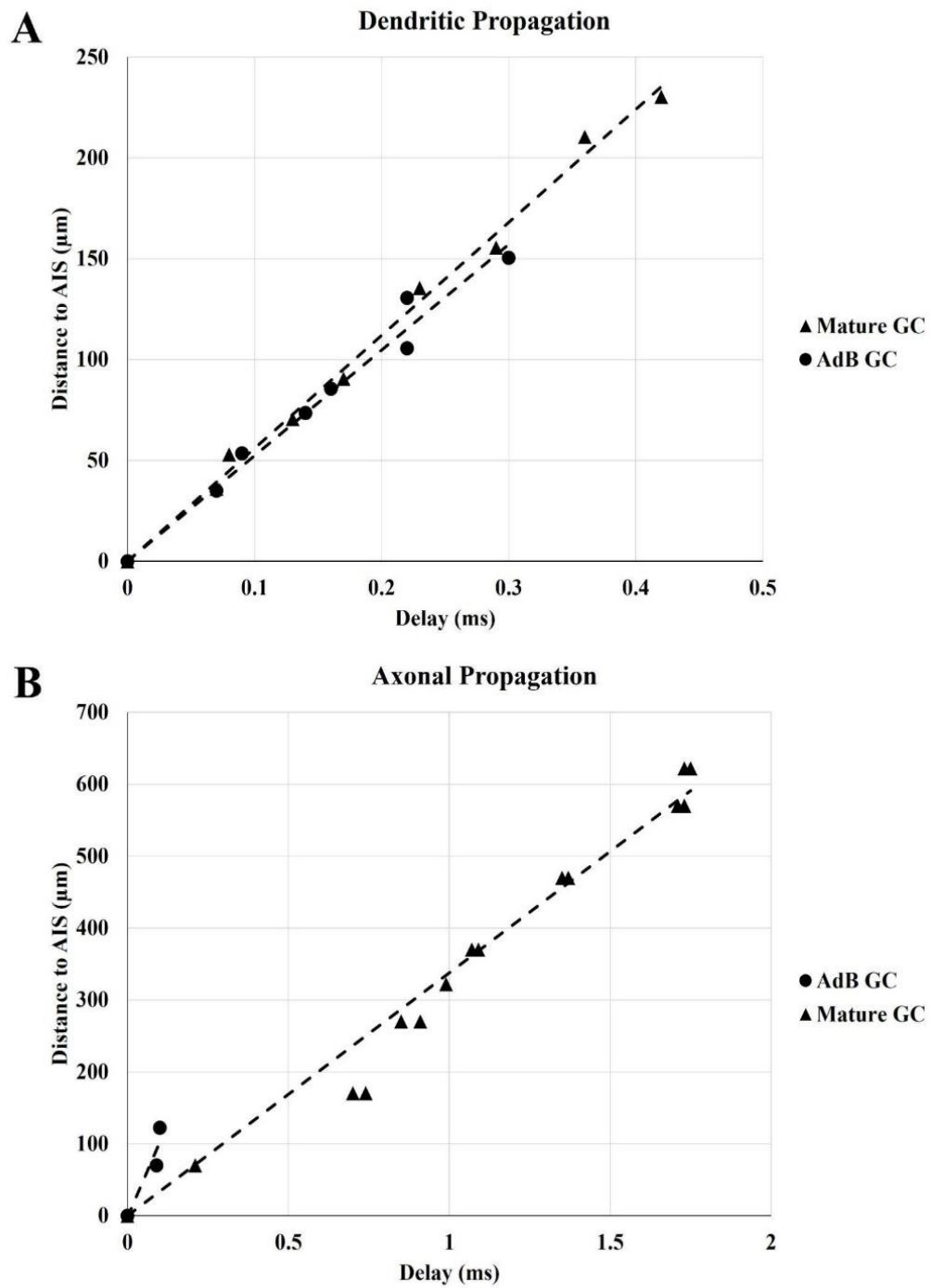


Figure 11: Delay–dependent distance (t,x) in action potential propagation for mature and adult-born granule cells.

The relationship between the propagation delay and the distance to the axon initial segment. Dendritic propagation is given in (A) and axonal propagation in (B).

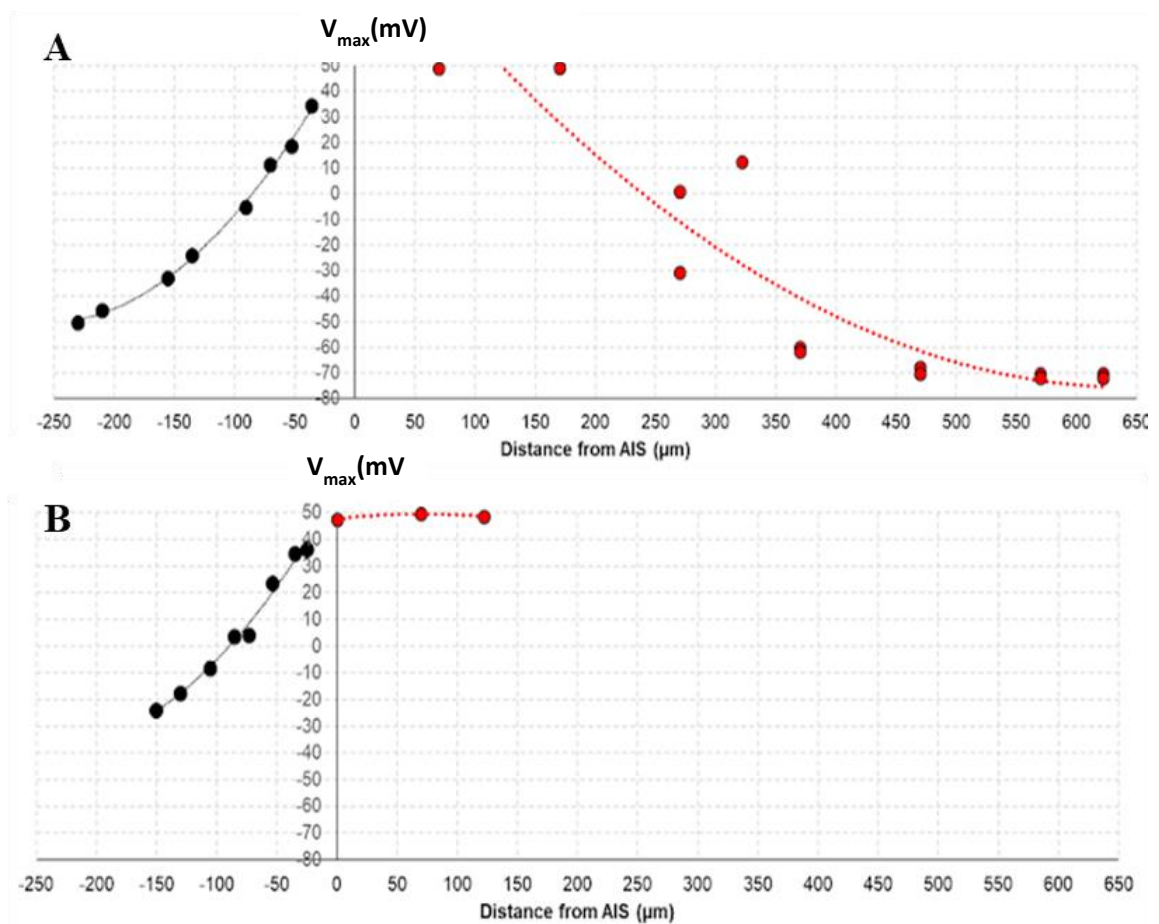


Figure 12: V_{peak} -dependent (t-x) distance in action potential propagation for mature and adult-born granule cells.

The dendritic and axonal action potential attenuation for (A) mature GCs and (B) young adult-born GCs.

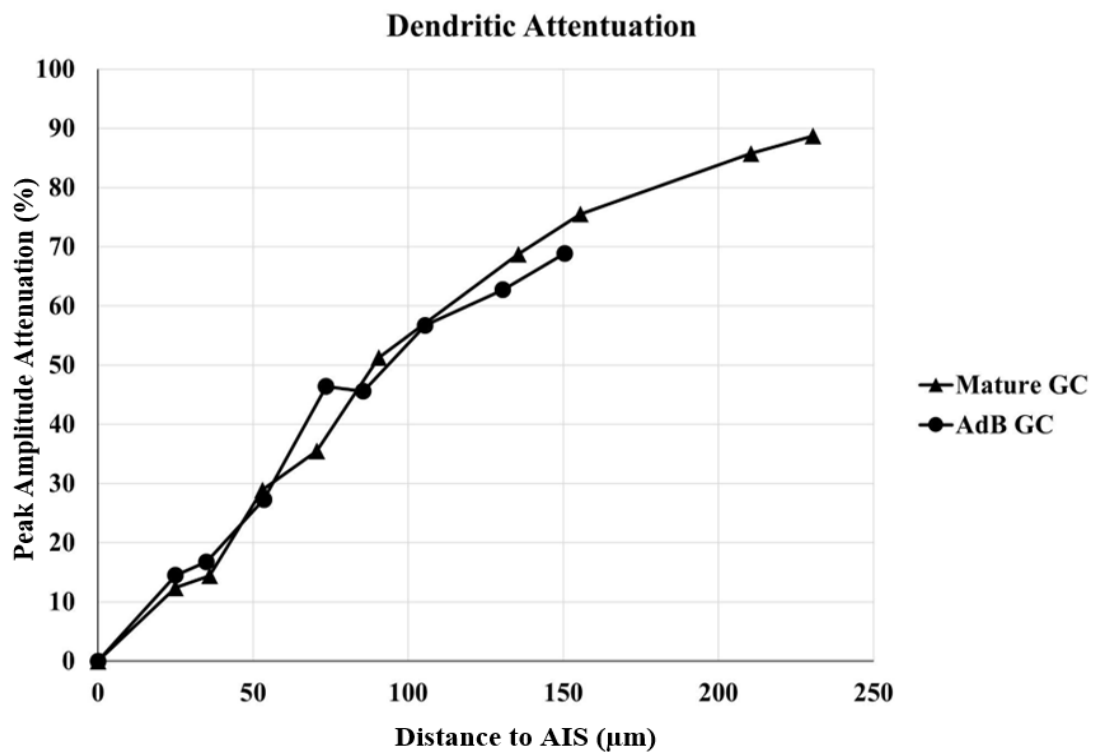


Figure 13: The dendritic peak AP amplitude attenuation in GC models.

4.4. Dynamic Gain Analysis

The dynamic response analysis is important for understanding how neurons respond to noisy input with varying frequencies. The gain represents the capacity for firing rate modulation in response to input frequency. Both models display a low pass filter characteristic in response to increasing f_I . The f_{cutoff} represents the frequency over which firing rate can not adapt to input frequency properly.

For both models, the parameters for noisy input current was not changed ($\sigma_I^2 = 0.01 \text{ nA}^2$, $\tau_I = 0.3 \text{ ms}$). The mean current (μ_I) was 0.268 nA for mature GC and 0.167 nA for AdB GC.

For AdB GC (Figure 14, red), f_{cutoff} is 100 Hz, which implies that the firing rate modulation in response to input frequencies higher than 100 Hz are attenuated. On the other hand, f_{cutoff} is 70 Hz for mature GCs (Figure 14, black). This result implies that AdB has the ability to respond higher frequency inputs more efficiently than mature GCs, and mature GCs selectively respond to lower input frequencies than AdB GC. AdB GCs might be attuned for higher frequency inputs while mature GCs respond to medium-sustained inputs. AdB GC exhibit lower gain at lower frequencies and this might imply that AdB GC has reduced adaptation to slow-sustained frequencies. Mature GCs are optimized for low-medium frequency inputs. These functional differences between AdB and mature GCs indicate that hippocampal network balance adaptability (via AdB GC) with stability (mature GC) which is critical for learning and memory.

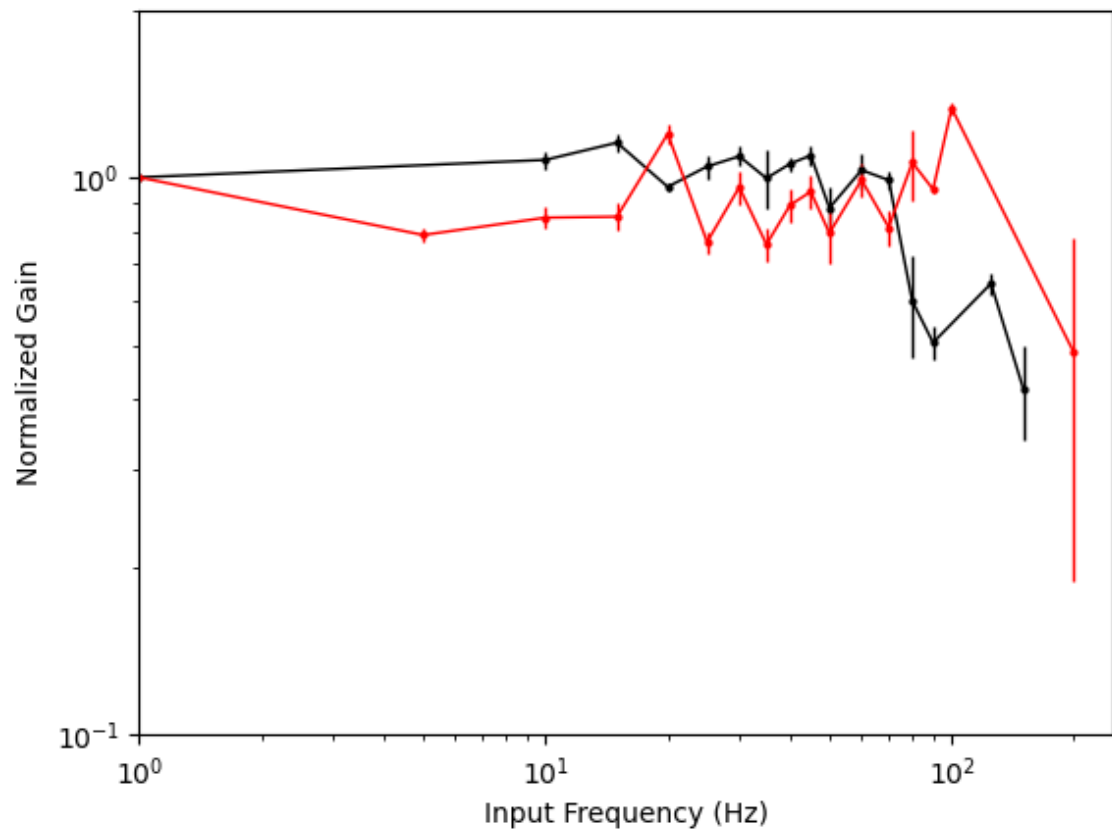


Figure 14: Dynamic Gain analysis plot.

The capacity for firing rate modulation in response to input frequency.

5. DISCUSSION

The goal of this study was to reveal how the distinct morphological features of AdB GCs impact the neural response characteristics. Towards this goal, we designed morphological conductance-based models of AdB and mature GCs. The most striking morphological difference between AdB and mature GCs is the length and branching of the axon (Zhao et al., 2006), which was reflected in the reduced topology of our models. Simplifying the actual morphology with identical biophysical parameters allowed us to eliminate the contribution of different biophysical properties of AdB and mature GCs and to emphasize the contribution of morphological properties.

Our results revealed that functional differences between AdB and mature GCs reflect their complementary roles in the hippocampal network. The threshold potential, V_{thr} , and the AP onset rapidness, ρ_{IFWd2} , of mature GC was higher than AdB GC. A lower V_{thr} implies that the action potential generation can be achieved with smaller oscillations in membrane potential. The higher onset rapidness implies a faster and more efficient response to fast-changing stimuli (Baranauskas et al., 2006; Öz, 2011; Öz et al., 2015). The phase plots also revealed faster depolarization and repolarization in AdB GC than mature GC. Vyleta and Snyder (2023) previously showed that mossy fiber terminals from AdB GCs are hyperexcitable in current injection experiments. They displayed a faster depolarization phase and were more excitable compared to mature GCs, which is in agreement with our findings. All these findings indicate that *the morphological differences between AdB and mature GC models are sufficient to reproduce the higher excitability of AdB GC.*

Another interesting finding was that AdB GCs can achieve similar firing rate as mature GCs in response to increasing constant input current. The somatic backpropagation delay, dendritic propagation and signal attenuation rates were also similar for both models. Brunner et al. (2014) found that a small soma and less extensive dendritic branching lead to lower capacitance, faster signal propagation, and response times in AdB GC, while mature GCs have higher capacitance, slower membrane time constants and signal integration. Schmidt-Hieber et al., (2004) determined that current threshold lower in AdB GCs (141 ± 12 pA $n = 4$) than in mature GCs (34 ± 9 pA $n=6$). A lower threshold current generally leads to a lower V_{thr} (Khodorov, 1974). These results agree with our findings that V_{thr} is lower in AdB GCs than mature GCs and AdB GCs are more excitable.

The propagation rates and frequency-current relationships in our models do not indicate a significant difference, which might be due to reduced biophysical characteristics. Thomas et al., (2009) used an adaptation of the SAS model which has detailed biophysical characteristics and concluded that changes in the sodium channel gating kinetics prolonged the duration of the GC response, whereas changes in the rapidly activated potassium channel gating kinetics modulated the GC firing frequency. This result was consistent with other reports in the literature (Tejada and Roque, 2014). The use of identical channel gating kinetics in our model might explain why we didn't observe a significant difference in f-I curves between AdB and mature GCs.

Interestingly, one important functional difference in our models was the f_{cutoff} . This result implies that AdB has the ability to respond higher frequency inputs more efficiently than mature GCs, and mature GCs selectively respond to lower input frequencies than AdB GC. AdB GCs might be attuned for higher frequency inputs while mature GCs respond to medium-sustained inputs. In line with our results, several studies that focus on biophysical characteristics rather than morphology also demonstrated that AdB GC responds to higher stimulus frequencies, whereas mature GC are less responsive at high frequencies (Ewell and Jones, 2010; Pardi et al., 2015; Beining et al., 2017). *The interesting conclusion from our models was that the morphological difference alone was able to explain, at least partially, this response difference between AdB and mature GCs.*

AdB GC exhibit lower gain at lower frequencies and this might imply that AdB GC has reduced adaptation to slow-sustained frequencies. Mature GCs are optimized for low-medium frequency inputs. These functional differences between AdB and mature GCs might imply that hippocampal network balance adaptability (via AdB GC) with stability (mature GC) which is critical for learning and memory.

For our goal, the use of HH model allowed for precise isolation of ionic dynamics because it provides a biophysically simplified conductance-based model. Keeping the biophysical parameters constant in both models was essential for isolating and addressing how distinct morphological features impact the neural response characteristics. Compared to more advanced models, such as T2N (Beining et al., 2017) and SAS (Santhakumar et al., 2005), our models certainly have limitations, e.g., *our model does not focus on biophysical properties where it focuses on morphological comparison.*

When AdB GCs mature, their excitability decreases (Brunner et al., 2014) and they become tightly coupled to inhibitory circuits. Their ability to refine glutamatergic connections are then limited. Furthermore, Temprana et al. (2015) show that AdB GCs more intensively engage in inhibitory feedback loops, which modulates the activity in GL. Together with the results presented in this thesis, these results provide insight into how AdB and mature GCs differ in their roles to contribute overall DG function and EChip circuitry.

6. CONCLUSIONS AND SUGGESTIONS

Morphological differences between mature and AdB GCs have been shown to have an impact on dentate gyrus functionality. In particular, structural differences such as dendrite branching and sizes of compartments have provided insight into how these cells play different roles in information processing.

Future research should focus on the axonogenesis and the maturation stages of AdB, as it would be helpful in understanding how the change of response and excitability during their integration into hippocampal network. Additionally, exploring how the ratio of AdB GCs in total GC population in DG influences the microcircuit response and hippocampal function can explain the balance between circuit stability and responsiveness. Investigating an optimal neurogenesis range may reveal critical thresholds for therapeutic interventions in conditions such as depression, epilepsy, and age-related cognitive decline. These questions can help future studies to uncover the contributions and functions of AdB GCs.

The thesis explores an important topic in neuroscience using innovative methodologies and has the potential to contribute significant insights to our understanding of adult neurogenesis and hippocampal microcircuits, with possible implications for neurological health and disease. Therefore, it should be considered for acceptance based on its potential contributions to the field.

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