MODELING NEURONS THAT CAN SELF ORGANIZE INTO BUILDING BLOCKS AND HIERARCHIES: AN EXPLORATION BASED ON VISUAL SYSTEMS

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ABSTRACT

MODELING NEURONS THAT CAN SELF ORGANIZE INTO BUILDING BLOCKS AND HIERARCHIES: AN EXPLORATION BASED ON VISUAL SYSTEMS

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Cell-cell and cell-environment interactions are controlled by a set of local rules that dictate cell behavior. With such local rules, emergence of computationally meaningful building blocks and hierarchies can be observed. For example, at the cellular level organization in the visual system, receptive field of a retinal ganglion cell displays an activation inhibition behavior that can be modeled as Mexican Hat wavelet or Difference of Gaussians. This precise organization is the product of a harmonious collaboration of different cell types located at the lower levels in a hierarchical structure for each ganglion cell. Moreover, a similar hierarchical organization is observed at higher levels in the visual system. This thesis investigates the visual system from several perspectives in an effort to explore the biological/computational principles underlying these local rules. The investigation results in a hybrid computer model that can combine the advantages of evolutionary and developmental principles to explore the effects of local rules on cellular differentiation, retinal mosaics, layered structures and network topology.

Keywords: *self organization, visual system, entropy, multiresolution*

ÖZ

ÖZDÜZENLEME İLE YAPITAŞLARI VE HİYERARŞİLER OLUŞTURABİLEN NÖRON MODELLENMESİ: GÖRSEL SİSTEMLER ÜZERİNE BİR ARAŞTIRMA

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Hücre-hücre ve hücre-çevre arasındaki etkileşimler, hücre davranışının belirleyicisi olan bazı yerel kurallarla konrol edilir. Bu kurallar ile, matematiksel ve berimsel olarak anlamlı bazı yapıtaşlarının ve hiyerarşilerin özdüzenlenmesini gözlemlemek mümkündür. Örneğin, görsel sistemde retinadaki ganglion hücrelerinin alıcı alanlarında gözlenen etkinleştirme baskılama davranışı Meksika şapkası (Mexican hat) dalgacığı (wavelet) veya Gausslar farkı ile modellenebilir. Bu etkinleştirme/baskılama davranışı daha alt seviyedeki farklı hücre tiplerinin bir arada uyum içinde çalışmaları sonucu ortaya çıkar. Ayrıca, benzer hiyerarşik özdüzenleme, görsel sistemdeki daha üst seviyelerde de gözlenir. Bu tez çalışması, görsel sistemi farklı yönlerden inceleyerek, özdüzenlemeyi sağlayan yerel kuralların altında yatan biyolojik ve matematiksel/berimsel prensipleri araştırmaktadır. Bu incelemenin sonunda, bu prensiplerden yararlanarak yazılan hibrid bir bilgisayar modeli kullanılarak, yerel kuralların hücre farklılaşması, mozaik retina, katmanlı yapı ve ağ topolojisine etkisi araştırılmıştır.

Anahtar Kelimeler: özdüzenleme, görsel sistem, entropi, çoklu çözünürlük

To my beloved family

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Many thanks to Assist. Prof. Dr. Murat Perit Çakır for his support, encouragement and guidance. Thanks to my brother and father for encouraging me on my computer model and allowing me to discuss with them any scientific idea. Thanks to my mother for always cooking exquisite and delicious meals. Thanks to my friend Engin for our conversations on Fourier transform. Thanks to all faculty members and all other friends for their comments and criticism on my thesis work.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

1 Introduction

Sophisticated organisms often display a well controlled complexity, regularity and hierarchical organization that emerge from cell-cell and cell-environment interactions. Brain and perceptual systems are the epitome of this phenomenon. A perceptual system transforms external stimulus into internal representation(s) while still mostly maintaining the spatio-temporal consistency within the transformed representation of the stimulus (i.e. a retinotopic map, see subsection 4.3.1). This “consistent” transformation often requires regularly organized computational “building blocks” (i.e. receptive field mosaics described in subsection 3.2.3) and, especially in the case of the visual system, a well organized hierarchical structure (subsection 4.1.1) that may be the result of information theoretic constraints (i.e. uniform sampling and joint entropy, sections 5.1 to 5.3).

Cell-cell and cell-environment interactions offer a way to understand how the organization of complex systems such as brain and visual system is controlled at cellular and hierarchical levels. These interactions can be described as local rules dictated by the DNA and epigenetic mechanisms. Local rules can be used in a computer model for modeling neurons that

can self organize into computationally meaningful building blocks and hierarchies that are observed in the visual system and brain.

Rigorous experimental analysis of various cell types (i.e. retinal ganglion cells, simple cells, complex cells described in sections 4.2 and 4.3) as well as computational and conceptual models make the visual system a relatively well documented area. Moreover evolution and development of visual systems are well studied. Therefore, an exploration of how visual systems evolve, develop and what the computational properties and constraints of vision are, may yield valuable information for a computer model. For this purpose, an investigation of evolutionary, developmental and computational principles underlying the organization of the visual system is required.

The quest for understanding the underlying principles of organization in the circuitry of visual system requires one to delve deep into the sea of knowledge within the territories of several disciplines. As visual system first decomposes visual input into its constituents, this thesis work, first starts with an analysis of the visual system from the evolutionary, developmental and computational perspectives. The analysis of the visual system spans the next three chapters. Each chapter represents insights and findings from a distinct perspective.

First, the chapter on the evolutionary perspective outlines the roots of synapse, neuron, the nervous system, eye and the visual system, and the biological diversity observed across the visual systems of primitive vertebrates in a comparative way. Then the chapter proceeds with a possible set of evolutionary mechanisms that may be responsible from the evolution of complex organs.

In the next chapter, a developmental perspective is adopted. Starting from the early development of the nervous system, processes such as cell proliferation, cell migration, axon guidance and cellular differentiation as well as programmed cell death and synaptic pruning are investigated. Next, the development of the retina, the visual

pathways and the developmental role of prenatal activity and postnatal stimuli are discussed.

In the third part of the analysis of the visual system, a conceptual/ computational approach is assumed. After starting with a review of well known conceptual/computational modeling paradigms developed for investigating the visual system, mathematical models of receptive fields of the cells in retina, lateral geniculate nucleus (LGN) and primary visual cortex (V1) are investigated. Then, in the discussion section, the modern view of visual system is compared to the traditional view.

In chapter 5, a synthesis of the highlighted points drawn from the previous three chapters is provided. The synthesis has revealed three fundamental principles which are relevant for modeling and investigation of computational properties of vision. These three principles are related to information theory, network theory and dynamical systems theory. For the first principle, information theoretic relation between entropy and visual pathways, the multiresolution scheme and its evolutionary advantages are discussed. For the second principle, the relation between the idea of reusability and systems displaying scale free network and small world properties are discussed. Finally, for the last principle, development, edge of chaos and dynamical systems are discussed.

In chapter 6, a hybrid computer model that was implemented to jointly explore evolutionary and developmental principles is given. In particular, within a computational framework, the effects of local rules are observed. Via successive addition of new rules to an initially simple computer model, different connection and cellular differentiation schemes, new cell types, mosaic and layered structures are observed.

Overall, questions such as “How visual system “acquired” the elaborate and precise organization through the evolution? What were the constraints and mechanisms? How visual system develops and how is complexity achieved during development? What are the relevant computational properties of vision? What is the author's overall computational perspective on the underlying principles?” are answered in

the next four chapters. Then an evolutionary developmental computer model, which embodies some of the design principles derived from previous chapters, is used for an investigation of local rules which define cellular interactions and their overall effects on cellular differentiation, mosaic and layered structures.

Main contributions of the computer model is that this model combines the advantages of *multi-objective optimization* and differential evolution (with modifications such as whole genome duplication, dynamic crossover rate etc., see subsection 6.2.3) with the advantages of developmental rules (regional identity, cellular differentiation, exclusion zones etc.). Since the design of the model is inspired from the evolutionary and developmental research on the visual system, the model generally uses biologically plausible principles. Moreover this model introduces a methodology to create/evolve cell types that can have highly specific behavior via successive addition of restrictive rules to the genome using an evolutionary component. This allows simultaneous existence of cell types that have different degrees of *precision* in their differentiation and connection scheme (subsections 5.1 to 5.3 are relevant). The model does not require predefined cell types except a single generic cell type. Therefore, in theory, this model can generate infinitely many number of cell types that can have separate differentiation and connection scheme. Using this model, one can create a network which incorporates various cell types that have certain characteristics similar to known biological structures (such as retina).

CHAPTER 2

2 Evolutionary Perspective

2.1 Origin of Nervous System

Research on many essential features of the nervous system shared by a wide spectrum of species points to a common ancestor that already had the *basic circuitry* (Ghysen, 2003). It seems there are few reasons for a developing organism not to use an already *well-tested* initial structure. If there is a highly selective pressure which requires a critical change, then a late modification to the initial structure is still possible.

From the developmental perspective, a well-tested fundamental circuitry is critical for an initial setting that allows later modifications to build upon it. Moreover, as time passes and evolutionary changes build upon the initial developmental trajectory (as later developmental modifications), a prominent change in the initial steps of developmental trajectory while maintaining stability would be less and less plausible (Ghysen, 2003). Therefore, rather than making an initial change, late modifications can be more robust. This idea explains the similarities between ontogeny and phylogeny. To give a well known example for *homology*, all tetrapods (vertebrates with four limbs) have five digits, yet they may be modified;

some digits may elongate and some may even completely disappear before birth so that they can be optimally used for various purposes.

Development of any complex organ *depends on* simpler and simpler versions of that organ along the (reversed) developmental trajectory. Thus, a late mutation that makes changes to the development of one of these simpler versions could disrupt the whole developmental trajectory (Andersen, 2003).

Brain and the nervous system also exhibits a complex structure and therefore the same idea applies. This motivates researchers to search for homologies between the nervous systems of species of extreme diversity. For example in a particular piece of research, the nervous system of flies (D*rosphila*) and humans are compared and it was shown that tripartite organization of brain and corresponding gene expression in the embryo of drosophila and human (or in fact any other vertebrate) is similar (Hirth *et al.*, 2003).

This suggests an *urbilaterian* ancestor (last common ancestor of all higher animals) that already had a nervous system with an *established degree of sophistication*. To have an idea on the nervous system of this urbilaterian ancestor, a finer grained analysis of the origins of nervous system is necessary. This requires an investigation beginning at least from the synaptic level.

2.1.1 Origin of Synapses: Ursynapse

Fundamental properties related to synaptic transmission and plasticity seem to be mostly conserved across species (Kandel, 2004). Therefore it is plausible to assume that there was a common ancestor which had the *ursynapse* (last common ancestor of all synapses) before an urbilaterian ancestor. Since without synapses, axons and dendrites are irrelevant, emergence of synapse seems to be a necessary precursory step for the evolution of neurons and therefore the nervous system (Ryan & Grant, 2009).

2.1.2 Origin and Evolution of Neurons

There are various theories on the origin of various aspects of neurons (Miller, 2009). According to one theory which dates back to 1970, a cell on a layer of tissue that can respond to physical stimuli by contraction may have been further specialized into two different cells, effectively creating two adjacent layers in which the outer layer of cells can detect physical stimuli and the inner layer of cells can contract. The communication between these adjacent layers may have been possible via ion exchange through pores. With evolutionary changes, the ion exchange mechanism may have turned into a more elaborate mechanism eventually creating synapses and later, axons and dendrites (Mackie, 1970).

The origins of excitability seem to date back to single-celled organisms. For example Paramecium caudatum uses electrical excitability as a *steering mechanism*. When it bumps into an obstacle, a voltage change occurs and its cilia movement changes for a short duration; as a result, the organism changes its direction (Miller, 2009).

At the genetic level, investigations of the *Amphimedon queenslandica (sponge)* genome points to a set of genes that are used in precursory neurons of more complex animals for differentiation. According to this body of research, this neurogenetic circuitry was ancient enough to be used by urmetazoans that are the first multi-cellular animals except sponges (Richards *et al.*, 2008). Moreover, it is well known that some sponges are able to generate action potential (Leys et al., 1999). Therefore, sponges seem to have many of the necessary tools for the evolution of neurons and the first primitive nervous system.

Another candidate proposed by some researchers is Ctenephores (comb jellyfish) which are considered as one of the first metazoans and they have a rudimentary net-like nervous system. However, genome analysis shows that the evolution of the nervous system of bilaterians (all higher animals) went in parallel with them (Schierwater & Kamm, 2010).

Nonetheless, simplicity of their neurons and their nervous system may highlight certain features that may also exist in more complex organisms.

2.1.3 Origin and Evolution of Eyes

From the evolutionary perspective, any organ with the ability to detect the direction of light can be considered as some form of eye such as an *imaging eye*, a *protoeye* or an *eye spot* (Lamb et al., 2009). There are also more strict definitions in the literature which requires eyes to be able to form an image, no matter how crude (Gregory, 2008).

Today, living animals have at least eight different types of eyes that can form an image. An animal may have either chambered or compound eyes that can use shadows, refraction or reflection for the formation of image (Gregory, 2008). What are the origins and mechanisms for the evolution of such diversity? To answer this question, one needs to first investigate the origins.

At the cellular level

First, photopigments bearing certain similarities to rhodopsin may have been evolved since they can be used by various single-celled organisms for purposes such as better harvesting light for photosynthesis and a better chance of finding mates or food. Research on phototaxis (which enables an organism to move towards the direction of light in three dimensions) confirms that this had indeed happened in eukaryotes *at least* eight times separately (Jékely, 2009).

At the multi-cellular level

Rather than creating novel solutions on the spot, gradual changes in *cellular specialization,* and therefore, *a* '*division of labor*' among different cell types is a more plausible scenario to explain the origin and evolution of the eyes. According to a recent research study, such a scenario may require a single multi-functional cell type that had the ability of *phototaxis* (Arendt et al., 2009). An ancient cell type that had cilia

movement, shading pigments and photopigments probably accumulated an initial toolbox of genetic information for the development of multi-cellular visual organization. Such a multi-functional cell may have been then evolved into several specialized cell types such as *shading pigment cells*, *photoreceptor cells* or *ciliated locomotor cells*. This idea predicts that certain vestigial features may still exist especially in larvae of certain animals. Supporting evidence for this prediction is illustrated in Figure 2.1 which shows multi-functional cells found in Amphimedon (demosponge) and Tripedalia (box jelly) larvae respectively. These cells can function as locomotor ciliated cells (LCC), photoreceptor cells (PRC) and shading pigment cells (SPC) (Arendt et al., 2009).

The compactness of the initial cell types and consequently the idea of an initial generic behavior for all cell types can be critical and will be used in the *evolutionary/computational model* (see chapter 6).

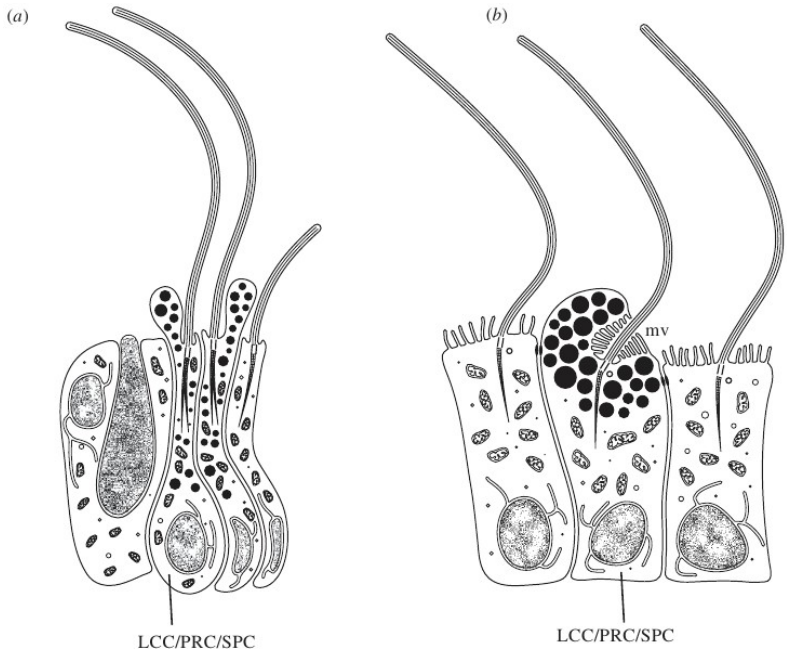

Figure 2.1. Multi-functional LCC/PRC/SPC cells

(a) Amphimedon (demosponge) larvae having only cilia (b) Tripedalia (box jelly) larvae having cilia and microvilli (mv)

(Arendt *et al.*, 2009, p.2810)

2.2 Linear Evolution

Sensory evolution requires a simple starting point. That is, through the evolutionary history, addition of '*sensory tasks*' on top of a primitive starting point is necessary (Nilsson, 2009). At first, ambient luminance may have been used to modify simple responses according to sea depth, time of the day etc.; then single purpose primitive sensory units *with peripheral filtering* may have been relevant for a simple processing circuitry or an effector organ. Only later, as the filtering and/or processing circuitry co-evolved with the sensory organ, responding to a larger variety of certain aspects of sensory input may have been possible.

2.2.1 Visual Acuity

As the evolution of the eyes continued, resolution of the visual input may have been a critical factor for predatory behavior, mate and/or predator recognition etc. For increased spatial resolution, narrower angles for each receptor cell may have been necessary. This may have been achieved by pigment-cup eyes at the cost of having less number of photons per photoreceptor. Although having membrane stacking may have increased the sensitivity to a small degree via increasing photoreceptive membrane area, focusing optics may have been the next necessary step to establish better sensitivity to low luminance and a high degree of spatial resolution (Nilsson, 2009). Overall, specialization of fundamental tasks in eye evolution may have followed below steps:

- Non-directional photoreception,
- Directional scanning photoreception,
- Membrane stacking (sensitivity to light),
- Spatial vision with low resolution,
- Focusing optics (higher sensitivity to light),
- Spatial vision with high resolution.

Visual acuity is probably a more stringent evolutionary constraint than one may expect, since the gradual refinement of the spatial resolution have certain computational implications. For example, evolution of better spatial resolution probably required more efficient mechanisms for the filtering and/or transformation of the visual stimuli. This and other computational implications of the evolution of visual acuity will be discussed further in chapter 5.

2.2.2 Earliest Vertebrates

Hagfish is a jawless vertebrate that survived for hundreds of millions of years without much change (Bardack, 1991). Hagfish eyes are fairly primitive since they lack cornea, iris and lens. Moreover its retina has only two layers instead of three, lacking bipolar and amacrine cells, consequently photoreceptor cells connecting directly to the ganglion cells (Lamb et al., 2007). Instead of a cornea, its eyes are completely *buried under a translucent patch of ski*n (Lamb, 2011).

Hagfish eyes may have been degenerated from a simple form of camera type eye. However, they seem to be still useful in their diminished form, since their eyes were maintained for millions of years without further decay. One theory is that hagfish eyes are used to *modulate circadian rhythm* (24 hour rhythm of bodily functions such as sleep etc) like the *pineal gland* in most vertebrate brain (Lamb, 2011). In fact, development of vertebrate eyes display a phase where the retina has only two layers, lacking bipolar cells, and photoreceptor cells connecting ganglion cells directly.

Hagfish eyes which are only used for detecting luminance (or non-directional photoreception) still have advantages. As one may expect, nondirectional photoreception seems to be the simplest possible form of vision. This supports Nilsson's theory (see 2.2.1) where he claims that specialization of fundamental tasks in the eye starts with non-directional photoreception (2009). After contrasting with Arendt and his colleagues research which was already discussed in section 2.1.3, one may conclude

that the earliest task of specialized '*eyes*' consisting of specialized cells that had lost their multi-functional properties was measuring ambient luminance (2009).

As the next step, for example a simple *sensor effector* circuit that could only be triggered by a specific form of stimuli may have been later evolved into a more multi-purpose system as the nervous system itself evolved into an elaborate structure which can process rather complex aspects of stimuli (Nilsson, 2009). This requires *cellular level* specialization. A supporting evidence for cellular level specialization in the vertebrate retina is based on rhabdomeric photorecepter cells, which are considered as the precursory cell that evolved into the retinal ganglion, amacrine and horizontal cells in the vertebrate retina (Arendt, 2003). Also rod cells are considered to be evolved from cones (Collin et al., 2009). Moreover, bipolar cells seem to be derived from rod/cone cells, explaining the close resemblance between bipolar cells and rod/cone cells (Lamb, 2011).

Overall, evolution of vertebrate eyes required cellular specialization and an increase in the number of layers in the retina. This idea may be critical for achieving a more sophisticated structure through the evolution[1].

2.3 Tree Thinking

Linear evolution models of eye can be further refined when combined with the concept of '*tree thinking*' (Plachetzki & Oakley, 2007). The rationale is that, since there is a common ancestor for most species, there should be several mechanisms to generate the observed diversity across species. Hybridization of ideas from linear evolution and tree thinking may bring a better explanation to the evolution of complex organs.

[1]Although the implemented evolutionary/developmental computer model (which will be discussed in chapter 6) is not a reverse engineering of retinal circuitry of the visual system, it supports cellular specialization as well as different number of layers.

2.3.1 Duplication, Divergence and Co-option

Proposed mechanisms by Plachetzki and his colleagues (2007) are *duplication, diversification and co-option*. '*Duplication*' applies not only to gen(om)e level duplications such as segmental duplication, whole genome duplication etc. but to any level such as cell, organ, protein domain, groups of interactive proteins etc. duplication. Similarly, diversification and co-option also apply to these levels.

To exemplify duplication and divergence, any serial homolog such as segments, limbs, teeth and eyes are considered diverging duplicates (Minelli, 2000). Duplications create redundancies which can freely be modified while the original copy can still maintain its tasks without any dramatic change or disadvantage, allowing *gradual* specialization.

In addition to duplication and divergence, there is another prominent mechanism called co-option. Co-option is in essence an *indirect* evolutionary mechanism, which is also known as exaptation (Gregory, 2008). Exaptation *recruits* already existing resources to solve a seemingly irrelevant problem. (Assembling several of such resources to create a novel functionality is called a *collage)*. An example to exaptation is that, due to changes in certain transcription factors, cells of certain types may be expressed in normally irrelevant positions (*ectopy*). *Recruitment* of these cells for the creation of a novel functionality would be exaptation *at the cellular level*.

2.3.2 Scaffolding

Scaffolding explains how organs having seemingly irreducible complexity can evolve. An architectural analog to scaffolding is given by Dawkins (1986, p. 149):

> An arch of stones...is a stable structure capable of standing for many years even if there is no cement to bind it. Building a complex structure by evolution is like trying to build a mortarless arch if you are allowed to touch only one stone at a time. Think about the task naively, and it can’t be done. The

> arch will stand once the last stone is in place, but the intermediate stages are unstable. It's quite easy to build the arch, however, if you are allowed to subtract stones as well as add them. Start by building a solid heap of stones, then build the arch resting on top of this solid foundation. Then, when the arch is all in position, including the vital keystone at the top, carefully remove the supporting stones and, with a modicum of luck, the arch will remain standing.

A summary of the proposed mechanisms which explain the evolution of complex organs is given in Figure 2.2 below. Stage (J) represents a seemingly irreducible complex organ in which all parts must be present to maintain functionality. At one step earlier there is (I) which actually has more components than (J). One component of (I) becomes unnecessary and lost, leaving behind an irreducibly complex organ (*scaffolding*). At an earlier step (H) is constructed via assembling (G) with (F) (*collage*). (G) has *duplicated* parts. (F) *modifies* the components it inherited from (E) for a better performance. (C) recruits (D) to achieve a new/better functionality creating (E) (*co-option*). (C) is again a *refinement* of (B) which is created by two irrelevant components in (A).

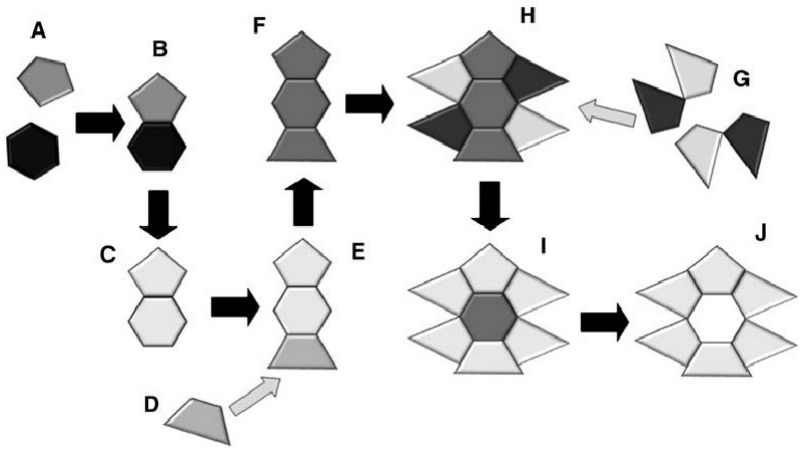

Figure 2.2. How to evolve a complex organ

(Gregory, 2008, p.365)

2.4 Summary and Discussion

The investigation of visual system from the evolutionary perspective, highlighted several critical biological properties. Three of them, which deserve reader's *further attention* will be discussed and summarized in this section.

Firstly, the mechanisms that explain the evolution of complex organs (discussed in 2.3) may as well explain how *a neural circuitry* that requires fast learning and/or optimization of a certain task, may have been evolved. Within the context of this thesis, referred neural circuitry corresponds to an efficient filtering and/or transformation mechanism for the visual stimuli, which should require a relatively short learning and/or optimization period. This entails that, there should be some mechanisms to organize *certain properties of the circuit before birth*.

An important evidence for this phenomenon is the observation that the development of '*receptive field mosaics of retinal ganglion cells*' (which provides uniform sampling for the visual space) does not depend on external stimuli (Anishchenko *et al.*, 2010). Therefore *receptive field mosaics of retinal ganglion cells* already matures before birth.

One regulation mechanism in prenatal retina is '*waves of activity*' which synchronizes retinal ganglion cells and their target cells. Results from related experiments indicate various signaling cascades which are controlled by several genes (Blankenship *et al.*, 2011, Torborg & Feller, 2005). However, environmental factors can also play decisive roles especially in *critical periods* (exemplifying *experience expectant development*). For example, postnatal visual circuit development has eye specific characteristics, since *experience dependent* pruning and axon refinement creates eye specific circuitry, which mostly requires external input (Huberman, 2007).

Also, to speculate from an evolutionary perspective, evolution of a *purely genetic* control mechanism that is responsible from a pre-optimized circuit which can consistently *segregate/integrate* input from both eyes

would be harder than evolution of a hybrid mechanism which partly depends on genes but can also take advantage of the *consistency within the external stimuli*. Thus, self organization of neural circuitry for visual system not only requires predetermined local rules which are modulated *by genes,* but also environmental inputs which have *intrinsic properties that can be exploited*.

Secondly, animals share a common urbilaterian ancestor and a common genetic toolbox for a primitive nervous system (Wirmer et al., 2012). These common genes used by both vertebrates and insects in the development and later functions of the nervous system. Pallium or cortex in vertebrates and mushroom bodies in insects have therefore a single evolutionary origin. It is obviously necessary to have novel proteins and genes to explain the extent of genetic diversity, however, it seems that diversity of phenotype is achieved via more subtle ways than simply adding one novelty after another. A relevant idea is that novelties are more in the form of new combinations of the common genes and timing of their expression in development. This may be because of the nature of a primitive system which gradually increase its complexity to gain new benefits while mostly keeping the previous advantageous structures (since there are no jumps in evolution). Therefore novelties depend on and *build upon* the ancient toolbox. This is why, in general, ancient genes have more than one functionality. They are refined, well-tested and used more commonly. In other words they are *reusable*.

Lastly, evolution of temporal and spatial visual acuity and acquisition of a more precise visual input have some information theoretic implications. These are closely related to the evolution of a *multiresolution scheme* which will be discussed in sections 5.2 and 5.3.

Overall, *a subset* of the key points highlighted in this chapter were:

- principles necessary for the evolution of complex organs,
- a body of evidence implicating an urbilaterian ancestor that had a relatively sophisticated nervous system and idea of reusability,

- evolutionary constraints on visual acuity and the information theoretic constraints on the processing/filtering circuitry.

This points have certain computational implications and they will be discussed in chapter 5.

CHAPTER 3

3 Developmental Perspective

3.1 Development of Nervous System

Neural development in humans starts from the third gestational week and arguably continues for a lifetime (Stiles & Jernigan, 2010). The developmental process is a complex harmony of both environmental and genetic factors, both of which have critical roles in the resulting neural circuitry via triggering of events or regulation between and within the developmental '*time windows*', which are illustrated below in Figure 3.1. Timing of events can be critical from the start, since early events trigger later cascades of events (i.e. regulation of cell metabolism affects cell cycles, cell cycles affect cell proliferation, cell proliferation affects migration and morphogenesis, migration and morphogenesis affect the development of the whole nervous system).

It is also crucial to see that some components of the genetic toolbox that are first used in the early stage of development later adopt new roles in specific contexts. Morphogens (which are discussed in subsection 3.1.2) are examples of this phenomenon, as they first function as guide molecules for migration, then pattern formation and cell fate. Later

however, they can be used in tasks such as axon guidance and the formation of neural circuitry.

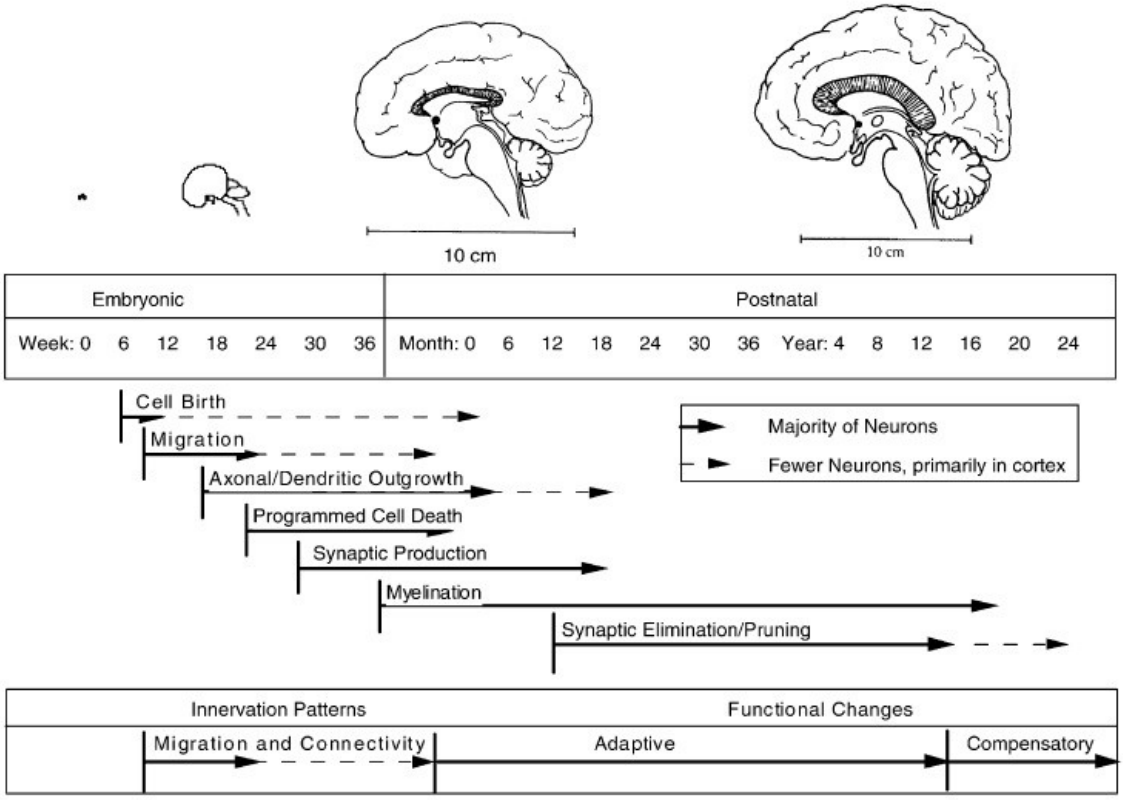

Figure 3.1. Developmental stages in human brain

(Andersen, 2003, p.5)

3.1.1 Early Stages

Neural development starts soon after the gastrulation phase, in which a single layer of germ cells in the shape of a hollow sphere which is called blastula, folds inwards and transforms into a three layered structure namely gastrula. After the formation of *notochord*, the earliest phase of neural development which is called neurulation begins.

Neurulation

Notochord can secrete several growth factors and also inhibitors which prevent the induction of an epidermial fate. Therefore, adjacent germ

cells in the ectoderm layer become neural progenitor cells and form the *neural plate* (Stiles & Jernigan, 2010). Neural plate first becomes *neural groove,* then by folding upon itself, transforms into *neural tube,* which is considered the '*primordium of the entire central nervous system*' (Greene & Copp, 2009). The period in which separation of neuronal cells from the ectoderm and morphosis of neural plate into the neural tube occurs is called *neurulation* and the developmental stage is called *neurula*.

The regulatory role of notochord remains essential throughout the neural tube formation and involves complex cascades of molecular signaling which control *cell behavior* and *pattern formation* (Stiles & Jernigan, 2010). Transcriptional networks and *biochemical gradients* play critical roles when controlling cell behavior. Recently, researchers have found another factor which is called transmembrane voltage gradients or V(mem). It turns out endogenous bioelectrical gradients can also play the role of an epigenetic regulator (Levin & Stevenson, 2012).

3.1.2 Morphogens

In a developing tissue, several signaling molecules (not necessarily proteins) are secreted for the regulation of neighboring cell behavior/specialization; some of these molecules can diffuse and form a *concentration gradient*, creating a coordinate system, which enables cells to assume a 'regional identity'[2] (Mason, 2009). These molecules are called morphogenes.

Morphogenes often have key regulatory roles. For example they are responsible from diversification of motor columns (Dasen & Jessell, 2009) and laminar structures as well as foliation and molecular organization of the cerebellum (Sillitoe & Joyner, 2007).

A relevant example to morphogens is called Sonic hedgehog (Shh). It plays key roles in many aspects of vertebrate development, such as dorso-ventral patterning of the developing neural tube and a direct effect

[2]Since it appears via morphogens, cells can assume a regional identity, the evolutionary/developmental computer model (discussed in chapter 6), allows progenitor cells in separate layers to initially have different cell type ids (before differentiation).

on axon guidance (McMahon et al., 2003). Moreover, Shh affects retinal ganglion cells. It turns out retinal ganglion axons need a precise regulation of Shh. That is, too high or too low concentrations inside the retina can disrupt the centrally directed axons of retinal ganglion cells (Kolpak et al., 2005).

Another example is Wnt, a family of secreted proteins. In early development, Wnt can *counteract* with Shh expression on the dorsal region of the developing neural tube (Robertson et al., 2004). Furthermore, Wnt proteins also have various effects on axons in different regions (Keeble *et al.*, 2006, Lyuksyutova *et al.*, 2003). In fact, Wnt and Shh are closely related, since they mostly *act in concert.* In late development, Shh and Wnt together can regulate neural circuit formation (Wilson & Stoeckli, 2012).

In summary, morphogens can regulate various early processes such as cell proliferation, migration, cell fate and tissue patterning and they can play key roles in later development such as neural circuit formation (Petrie et al., 2009).

3.1.3 Cell Proliferation

Cell proliferation or reproduction begins with neural tube closure. Cell division always occurs at the inner surface of the neural tube (*ventricular zone*). Two types of cell division is possible. In *symmetric cell division,* two daughter cells remain in proliferative state. In assymmetric cell division, one daughter cell remains proliferative, the other *migrates away* from the neural tube. Some of these cells become neural precursors (neuroblasts), while others become glial precursors or glioblasts (Kriegstein et al., 2006). In proliferation phase, one mother cell can produce as much as ten thousand daughter cells (thousands per minute).

3.1.4 Cell Migration

Cell migration in vertebrates mostly uses molecular mechanisms which were long before used by simpler organisms (Hatten, 2002). This

complies with the idea of *reusability* in evolution (described in 2.2.1), since there is no reason for a complex organism not to use an already *well-tested* toolbox of genes which control initial phases of development, even if this toolbox is inherited from much simpler organisms.

Directionality

The migrating cells often have an asymmetric morphology which allows researchers to define a leading and a trailing edge (Petrie *et al.*, 2009). Therefore, when there is a cue for migration without any available directionality information (*motogen*), direction of the cell migration only depends on this intrinsic asymmetry (*chemokinesis*) (Stoker & Gherardi, 1991).

In cells having no intrinsic asymmetry, the movement is random (Petrie *et al.*, 2009). However, when there are external signals regulating directionality, (asymmetric cues such as external biochemical gradients), migration of the cells are controlled via an '*internal compass*', or a steering mechanism that can make use of these external cues (*chemotaxis*) (Arrieumerlou & Meyer, 2005). With combinations of several such cues, regulated directionality information can have anterior-posterior, dorso-ventral or radial characteristics (Hatten, 2002).

Neuronal cell migration

Long radial glia connect inner (ventricular zone) and outer surfaces (mantle zone) of neural tube. On the surface of radial glia, there are certain cues that regulate the migration of cells from ventricular to mantle zone (*glial mediated migration*). Another mechanism of migration is also possible, where first an extension towards mantle zone is created and then cell body follows (nucleokinesis & *somal migration*). Overall, neuronal cell migration has radial characteristics (Nadarajah *et al.*, 2001).

3.1.5 Development of Cortical Layers

Cortical layers develop inside out. That is, earliest neurons migrate to the deepest cortical layer. With next waves of migrations bypassing the earlier layers, more superficial layers successively develop (Stiles & Jernigan, 2010). Note that migrating neurons have no axons or dendrites. Development of cortical layers is illustrated in Figure 3.2 in more detail.

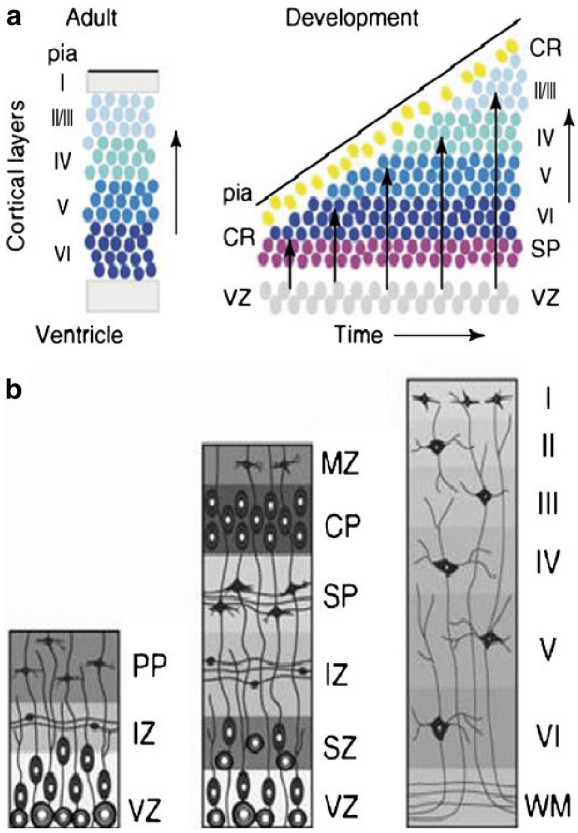

Figure 3.2. Development of cortical layers

(a) As time passes, superficial layers develop, (b) Neurons first migrate from ventricular zone (VZ) and form preplate (PP), then the next wave of migrating neurons splits PP into marginal zone (MZ) and subplate (SP) which are *transient* brain structures. Mature brain does not have MZ,SP or VZ. Intermediate zone (IZ) becomes white matter layer (WM), Cajal-Retzius (CR) cells produce *Reelin* which is a cue for the migrating cells to stop.

(Stiles & Jernigan, 2010, p.337)

3.1.6 Cellular Differentiation

Cellular differentiation is specialization of progenitor cells into more specific cell types. It is closely related to proliferation.

Research on progenitor cells shows that early in development they can produce any type of neurons. However, at later steps progenitor cells generate only region specific cells and by the end of neurogenesis, they are '*lineally commited*' to upper layer cells, supporting the idea of *fate restriction*[3] (Desai & McConnell, 2000).

Through the development, different morphogens and mitogens (triggers of mitosis) are produced; they can have prominent effects on *cell cycle*, *proliferation and differentiation*. Some of these are well known, common regulators of differentiation (such as *Notch*, *Wnt*, FGF, *Shh*) and transcription factors (such as Sox family, Oct4 (Pou5f1) and Myc) and others are specific neurodevelopment transcriptional regulators (such as Hes, Neurogenin, Math and Mash1) (Kaldis & Richardson, 2012). For neural development, combinations of above signals and certain epigenetic mechanisms control cell cycle parameters, proliferation and differentiation.

3.1.7 Axon Guidance

After migrating neurons reach their target region, they develop axons and dendrites. Dendrites form dense arbors. Axons elongate and extend, *growth cones* at the tip of axons move towards their targets using cues such as attractive and repulsive guidance molecules which may be diffusible or may require contact. There is a *fine grained* resolution for the interaction of growth cones with cue expression; that is, there are '*hot spots of cue expression*' (Mason, 2009). Moreover, *transcription factors regulate* the guidance *receptor* and *cue* expression. Therefore same cue may be interpreted as either repulsive or attractive according

[3]This idea and idea of regional identity described in section 3.1.2, are used in the computer model (discussed in chapter 6) as layers where each layer contains only a subset of overall cell types.

to the receptor. Some of the well known guidance cues and their receptors are given below:

Table 3.1. Axon guidance molecules

Guidance Cue	Secreted/Membrane	Repel/Attract	Receptors
Netrin	+	+,-	DCC,UNC5
Sli	+	+	Robo
Ephrin	-	+,-	Eph,Ephrin
Semaphorin	+,-	+	Plexin,Neuropillin
CAM	-	+,-	CAM
Morphogens: BMP,*Wnt*,FGF and *Hedgehog*	+	~,+,-	Ryk,Frizzled

+ first is true, - second is true, ~ concentration specific

Also known are neurotransmitters like GABA, ECM (*extra cellular matrix*) molecules such as laminin, and growth factors like NGF (Bear et al., 2006, p.699). These neurotransmitters and growth factors are used for either refinement in the axon navigation or stability of newly made connections.

Also note that researchers believe the first growing axons use surrounding cells as guides. However, later axons may not need to use surrounding cells at all; especially if they are *forming bundles*, they simply grow along with their mates (Mason, 2009). Moreover growth cone behavior may change in *mid-development* according to the changes in receptor expression.

3.1.8 Programmed Cell Death

As a natural phenomenon, at least fifty per cent of synaptic connections and a similar rate of neurons is eliminated in a systematical way in the developing brain (Stiles & Jernigan, 2010). In some regions, the rate is as high as seventy per cent (Rabinowicz *et al.*, 1996). Neuronal loss mostly

occurs prenatally, while pruning of axons spans a larger timescale and it is mostly postnatal. For programmed cell death, a gene regulated mechanism called *apoptosis* which consists of a series of physiological events that describes an intrinsic suicide program is used.

Apoptosis can be triggered by various environmental factors as well as cell intrinsic ones. Likewise, apoptosis can also be prevented by several factors. For example, *neurotrophic factors* protect the cell from apoptosis. These factors are mostly produced by target neurons. A 'successful' afferent neuron is granted neurotrophic factors at synaptic sites which are used 'effectively' (Huang & Reichardt, 2001). Therefore, there is a *high stake competition* between neurons to establish effective connections since survival of the neurons is directly influenced by the amount of neurotrophic factors[4]. Cells which are solely used for 'construction' or cells that have *transient roles* in development can be eliminated via apoptosis after they have fulfilled their tasks. Consequently, apoptosis rate is also high in neural progenitors (de la Rosa & de Pablo, 2000).

3.1.9 Synaptic Elimination/Pruning

Developing neurons make extremely abundant amounts of synaptic connections. Although this may provide an initial advantage for the *development* of robust and malleable circuits in prenatal and early postnatal periods, at later phases in development, a more precise circuitry is favored. Therefore initial number of synapses in an infant brain, which has double the number of synapses compared to an adult brain, slowly declines with childhood and adolescence (Stiles & Jernigan, 2010).

Similar to the *transient cells,* which have a scaffolding role in prenatal development, *transient connections* are observed in infants. For example, pathways having such a role are observed between/within corpus callosum, thalamocortical pathways, cortico-spinal tract, as well as

[4]This idea was used in the evolutionary/developmental computer model discussed in chapter 6.

temporal lobe and limbic system (Stiles & Jernigan, 2010, Innocenti & Price, 2005).

Pruning and neurotrophic factors are closely related. For example, competition between synaptic connections for neurotrophic factors is a prominent mechanism for pruning. This also puts the role of external stimuli in the picture since afferent input may be critical to stabilize certain pathways.

At the microscale, researchers show that there is a highly balanced dynamism at work. For example, rapid sampling, synapse formation and retraction are supporting mechanisms for axon guidance and target detection (Hua & Smith, 2004).

3.2 Development of the Visual System

How does the visual system achieve a well organized circuitry? The same principles for the development of nervous system apply. How does the visual system further refine the circuitry and achieve more precision? Answering this question requires one to look into the development of retina and then investigate the roles of prenatal development (internal stimuli) and postnatal development (external stimuli).

3.2.1 Development of Retina

Retina has at least seven major cell types (rod, cone, amacrine, bipolar, horizontal, ganglion and Müller glial cells) and production of each cell type in right ratios requires a regulation at the proliferation stage (with the exception of ganglion cells whose number is regulated via programmed cell death).

After progenitor cells produce these cell types, migration into a correct location is the next necessary step. Migration into three distinct layers of retina occurs mostly as *somal migrations* (see 3.1.4). Meanwhile, before ganglion cells reach to their final positions, their axons already develop and extend across the inner retinal surface (Reese, 2011). After

postmitotic cells position themselves into their destinations, their *anchoring radial connections* are lost (Ford & Feller, 2012).

Next, axon and dendrite growth occurs and inner plexiform layer (IPL, connection site of retinal ganglion, amacrine and bipolar cells) and outer plexiform layer (OPL, connection site of rod and cones, bipolar cells and horizontal cells) in retina develops (Morgan et al., 2011). First, retinal ganglion cells and amacrine cells form the earliest functional circuits in IPL. Then, horizontal cells and photoreceptors connect to each other, forming OPL.

At this stage, there are *transient* connections between photoreceptors and ganglion cells. Therefore, early in development, retina has a primitive form (probably reminiscent of an earlier ancestor) having two layers instead of three. Only later, bipolar cells (as mentioned earlier in 2.2.2) are created and they migrate between IPL and OPL. Then axons of bipolar cells connect to IPL and dendrites connect to OPL detaching the two layers and causing the ganglion cells to lose the transient direct connections to photoreceptors (Lamb, 2011). In the final step, synchronization between and within layers (lateral and vertical organization) and synaptic elimination occurs.

3.3 Development of Thalamocortical Pathway

The *thalamocortical (TC) pathway* transmits sensorimotor information (retina, cochlea, muscle or skin) to neocortex via the thalamus. It develops starting from the later part of the second trimester in humans till 26th gestational week (Kostović et al., 2006). The *subplate layer* (which is a transient structure observed in prenatal development, see 3.1.5), has a role in the construction of the TC pathway. Initially TC axons connect to the subplate layer and the subplate layer axons connect to the real targets of TC axons in cortical layer 4 (which is the primary input layer). With the help of subplate neurons, normal patterns of TS pathway develop. Only after around *four weeks*, the TC pathway becomes

complete and subplate neurons start to gradually remove their connections and eventually die (Stiles & Jernigan, 2010).

3.3.1 The Role of Prenatal Activity

Researchers show that *prenatal retina* already develops similar '*receptive field mosaics*' to adults; that is, receptive field center distribution and receptive field overlap distribution of ganglion cells are already fairly developed *before birth* (Anishchenko *et al.*, 2010). One explanation is that in the prenatal retina, there are spontaneous patterned waves of activity. Such activity may effectively refine connections in an orderly way to represent maps of sensory space (Torborg & Feller, 2005). It was already observed decades ago that prenatal retinal ganglion cells activate (almost once per minute) in a periodical manner (Galli & Maffei, 1988). It turns out, the activation of ganglion cell can propagate from one cell to the next like a wave. This phenomenon is observed in various forms such as

- *embryonic waves* (which use gap junctions or electrical synapses),
- *cholinergic waves* (which use chemical synaptic transmission),
- *glutamatergic waves* (observed mostly in postnatal development, use of glutamate in synaptic transmission; also unlike the first two, waves observed within only a subset of neighboring cells (mostly OFF cells)).

Above mechanisms may contribute to the development of dendritic maturation of ganglion cells which will become '*committed to*' one of ON-OFF layers (only responding to either onset or cessation of light respectively) which are physically segregated from each other (Ford & Feller, 2012). This is called ganglion cell stratification. In fact, there is supporting evidence that *cholinergic waves* have a role in ganglion cell stratification (Bansal *et al.*, 2000). However, cell stratification does not explain how receptive field mosaics develop before birth.

Another possibility is that instead of retinal waves, receptive field mosaic formation may be primarily determined by the formation of *anatomical mosaics*[5] (Anishchenko *et al.*, 2010). A proposed theory is that anatomical mosaic formation can be achieved via type-specific neighboring cell interactions (Fuerst et al., 2008). Live imaging studies support this view since repulsive interaction between the same cell types are observed. For example most retinal ganglion dendrites avoid the dendrites of the same type (Lohmann et al., 2001).

Overall, the *prenatal development* of the retina seems to rely on both retinal waves and *construction rules* which intrinsically enable the creation of anatomical mosaics and stratification.

3.3.2 The Role of External Stimuli

From the beginning of prenatal period till opening of eyes, several refinements are already made and consequently some characteristics of visual circuitry are already in mature form (McLaughlin et al., 2005, Chapman, et al., 1996). However, although connections are well patterned and some have even matured, there are still connections which are mostly malleable.

Light sensitivity and visual acuity increases with postnatal adjustments and/or refinements to certain characteristic of some cell types, for example the receptive field properties of neurons in the visual system. Therefore external stimuli become critical on the maturation process of visual circuitry. While axon guidance cues, some signaling cascades and certain regulatory molecules still have roles on postnatal development, spontaneous neural activity becomes most prominent for the maturation of receptive field structures for neurons in various hierarchical levels.

These receptive fields together define a circuitry for feature maps such as retinotopic maps (Huberman et al., 2008). A well balanced and mostly segregated eye specific circuitry also develops with external stimuli

[5]The idea of anatomical mosaics is used in the evolutionary/developmental computer model (see chapter 6).

(*ocular dominance columns* and eye-specific layers). Spontaneous activity (retinal waves) and external stimuli in critical periods allow the visual circuitry to achieve more precise connections and an overall refinement. Certain molecules quicken this process by translating activity into structural changes (Stevens *et al.*, 2007).

While the effects of external stimuli can be critical for the development of certain characteristics, as mentioned earlier, not everything is activity dependent. Layer formation, overall map layout and retinal map mosaics (subbsection 3.2.3) are stereotyped features which are effectively controlled by genes and they mostly do not require external stimuli.

3.4 Summary and Discussion

The investigation of visual system from the developmental perspective, highlighted several critical biological properties. Some of them, which deserve reader's *further attention* will be summarized and discussed in this section.

Firstly, it is evident that genes have *strong control* on the development of nervous system (see Morphogens under 3.1.2). Therefore, cellular (self) organization strictly depends on genes. However, this does not necessarily mean that the process of neural developmental is a strictly deterministic one. On the contrary, development *per se* may have certain *chaotic* characteristics, especially due to epigenetic factors. For example, no identical twins have the exact same fingerprint, nor have the exact brain structure. That is, regarding both fingerprints and brain structures, identical twins can have different 'folds' (*gyri&sulci*). Yet, the chance that they have the same fingerprint '*type*' (used in pattern recognition) is much higher (0.7440) than non-identical twins (0.3215) (Tao et al., 2012). Likewise, similarity between brain scans of identical twins is much more significant, when compared to non-identical twins (Thompson *et al.*, 2001, Pell *et al.*, 2010).

Secondly, regarding the evolution of complex 'organs' and evolutionary constraints, (see 2.3), events in the developmental trajectory may *build*

upon each other and changing the genetic toolbox that controls *early events* may become harder and harder while an organism evolves and becomes more complex. For example, proliferating cells use aerobic glycosis (2 ATPs), rather than using oxidative phosphorylation (36 ATPs) to generate energy (*Warburg effect*). The answer to the question, why they use this inefficient mechanism even with abundant oxygen, lies in the fact that proliferating cell growth machinery *needs* a high ATP/ADP ratio and certain 'metabolic requirements that extend beyond ATP' (Vander et al., 2009). To speculate from evolutionary perspective, one prediction would be that proliferating cells still *depend on* a machinery that was 'invented' long before oxidative phosphorylation.

Thirdly, the similarity between axon guidance and cell migration (discussed in 3.1.4) is hard to miss. It is highly plausible that cell migration contributed to the evolution of axon guidance. A relevant work which compares the underlying signal transduction pathways of neural growth cones with migrating cell types (dictyostelium, neutrophils and fibroblasts) supports this idea. It turns out that axon growth shares some "*conserved mechanisms* such as localized PI3 kinase/PIP3 signaling and a common output, the regulation of the cytoskeleton by Rho GTPases" (Philipsborn et al., 2007). From the evolutionary perspective, this may be a relevant example for exaptation (recruitment and usage of an earlier functionality in a different context which was discussed in 2.3.1). Also from the developmental perspective, a prediction is that *transmembrane voltage gradients* (which are epigenetic factors that function similar to morphogens, discussed in 3.1.1) may have a role in *axon guidance*, probably as a cue that provides local information (spatio-temporal) on *neuronal activity*.

As a conclusion, controlled yet chaotic characteristics of development and reusable nature of genes deserve further attention and their computational implications will be discussed in chapter 5.

CHAPTER 4

4 Conceptual/Computational Perspective

Since the extensive research of Hubel and Wiesel on *receptive field* properties of the cells in the primary visual cortex of various animals, the visual system drew the attention of a progressively more number of researchers from various disciplines (Hubel & Wiesel, 1962). The term *receptive field* which was first used in the early studies of retina, now has a more general meaning (Martinez et al., 2003). If a stimulus on a spatial (and temporal) region can change the behavior of a cell (not only retinal cells but also cells of higher levels, as well as cells of different sensory modalities such as the sense of touch); then the region is considered within the receptive field of the cell.

Ideas of Hubel and Wiesel rightfully dominated the field for decades because of the systematic nature of their work and the resulting hierarchical model. Therefore this chapter will start with a review of the traditional perspective. Then, mathematical models which mostly incorporate traditional ideas will be given. Finally, at the end of the chapter, recent contributions and a comparison between the traditional and the modern view will be made.

4.1 Comparison of Models

There are three well known frameworks that contribute to the overall view of how the visual system works. Hierarchical model will be discussed first.

4.1.1 Hierarchical Model

Mathematical models are heavily affected from the traditional hierarchical understanding of visual system. Thus, the hierarchical model of Hubel & Wiesel will be discussed first (Figure 4.1).

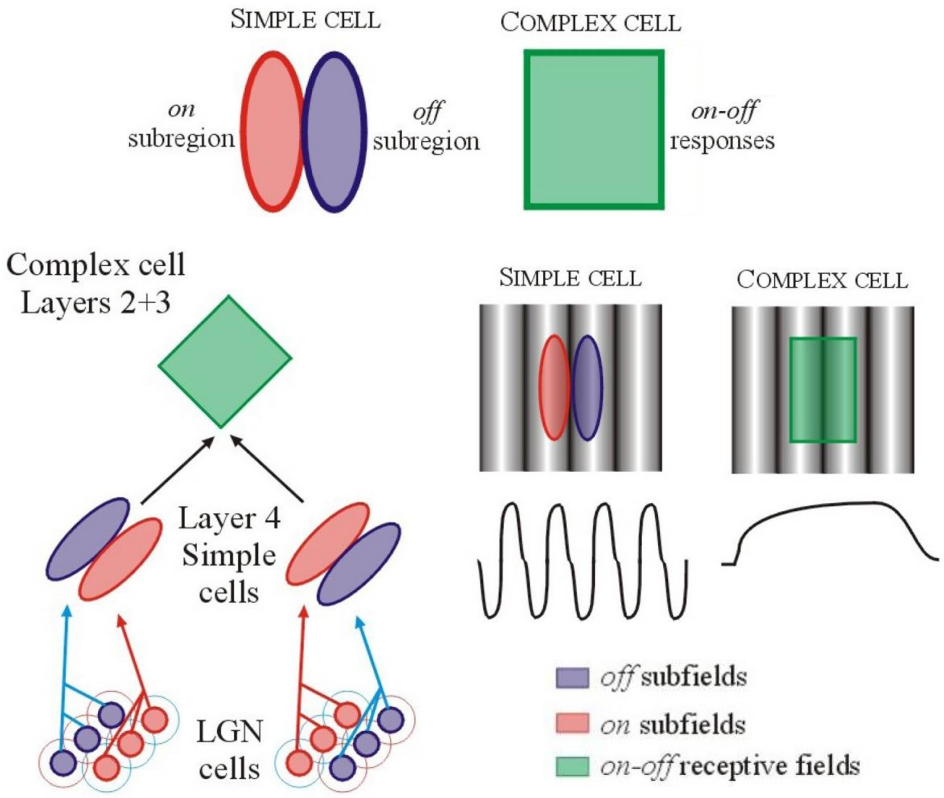

Figure 4.1. Simple and Complex cells in Hubel & Wiesel's model

(Martinez & Alonso, 2003, pp.317-331)

Hubel & Wiesel's idea was that receptive fields of simple cells were resulted from the center-surround receptive fields of aligned lateral

geniculate nucleus (LGN) cells. Complex cells which were considered at the top of the hierarchy (layer 2 and 3), received only input from simple cells with similar orientation selectivity from layer 4.

According to Hubel & Wiesel, simple cells had common characteristics such as:

> 1. they were subdivided into distinct excitatory and inhibitory regions
>
> 2. there was summation within the separate excitatory and inhibitory parts
>
> 3. there was antagonism between excitatory and inhibitory regions
>
> 4. it was possible to predict responses to stationary or moving spots of various shapes from a map of the excitatory and inhibitory areas. (Hubel & Wiesel, 1962, as cited in Martinez et al., 2003, p.318)

Complex cells had not been classified according to their common characteristics (which were little), instead, they were the cells that did not fit above characteristics. Later, quantitative methods (i.e. response modulation) were developed to make a better distinction between the two cell types (De Valois et al., 1982).

In the hierarchical model, only simple cells received input from LGN cells and complex cells being at higher levels of the hierarchy were assumed to have no direct connections from LGN cells. However, later studies suggested that this was not the case and there were direct connections (Martin et al., 1984).

Yet, some computational models supported Hubel & Wiesel's ideas. First, energy models arose. Complex cells were modeled as “square sum of simple cells with similar orientation and spatial frequency but with phases that differed in 90 degrees”. (Ohzawa et al., 1990, Shams & von der Malsburg, 2002, as cited in Martinez et al., 2003). The energy models all assumed successive stages and therefore an underlying hierarchical model.

4.1.2 Parallel Model

Since it was demonstrated that complex cells also receive input from LGN, some researchers suggested separate channels where complex and simple cells work in parallel (Stone et al., 1979). They argued that nonlinearity started from retina and complex cells did not need input from simple cells to achieve their nonlinear behavior.

Parallel model was supported by some experiments in which complex cells were activated yet simple cells were not (Hammond et al., 1977). However, the idea that complex cells were completely independent from simple cells was also refuted by some researchers (i.e. Callaway, 2001). Computational models that supported the parallel model were suggesting that LGN input with overlapping on and off centers could create orientation selectivity with insensitivity to phase changes (phase-invariant orientation tuning) (Mel et al., 1998).

4.1.3 Recurrent Model

Being a more modern approach, advocates of the recurrent model pointed to the discovery that the number of synapses between cortical regions and cells were much larger than the number of synapses coming from LGN (Martinez et al., 2003, Ahmed *et al.*, 1994, Martin, 2002). In the recurrent model, it was proposed that intracortical connections may play the role of an amplifier for the weak percentage of input (10%) coming from LGN (Peters et al., 1993). Therefore the idea that a modulation of linearity by mainly cortical components is plausible. However, as the complexity of the model increases the amount of possible computational models with different perspectives also increases (Somers et al., 1995, Martinez et al., 2003).

Overall, above models highlight certain properties of vision and these properties are not necessarily mutually exclusive (Martinez et al., 2003). Consequently, a more generalized model that takes into account *processing modes* which are specific to task types, would draw ideas from all three models.

4.2 Retina

Visual processing starts with the retina. There are several types of cells each mostly specialized on a single task. They function together in both parallel and hierarchical ways. For example there are cells specialized for color and detail as well as there are cells specialized for light sensitivity. Photoreceptors which are called rods are very sensitive to light and mostly insensitive to color. Counter intuitively, photoreceptor cells are depolarized in the dark (Schnapf et al., 1987). This means that photoreceptors are excited in the dark and inhibited in the presence of light.

When light levels become low, rods become active. Cones on the other hand, work best in daylight since they are less sensitive to light than rods and more sensitive to color. In fact, this specialization of cells into opposite tasks is observed also in other levels of the retina and throughout the visual system. However, the role of retina is not only to segregate the visual input into its constituents, but also to function as a filter, reducing the redundancies within the stimuli. Photoreceptor cells (and some retinal ganglion cells) absorb the light and this initial signal is preprocessed via bipolar, horizontal and amacrine cells in a hierarchical way before it reaches most of the retinal ganglion cells. These cells together construct the *receptive fields* of retinal ganglion cells. Receptive fields have certain mathematical properties and they can be studied with formal approaches.

Although in reality, there are more than twelve retinal ganglion cell types, in the traditional view of the visual system, retinal ganglion cells are divided into two major categories according to their size: magnocellular and parvocellular cells (Figure 4.2). Magnocellular (M) cells are large and insensitive to color, they also have large receptive fields and they can transmit information at a faster rate than parvocellular (P) cells. M cells can be further classified into two basic functional types. The first type, which is called on-center type, is inhibited if light falls on the

surround, and activated when light falls on the center. The second type is called off-center type and it acts in the exact opposite way.

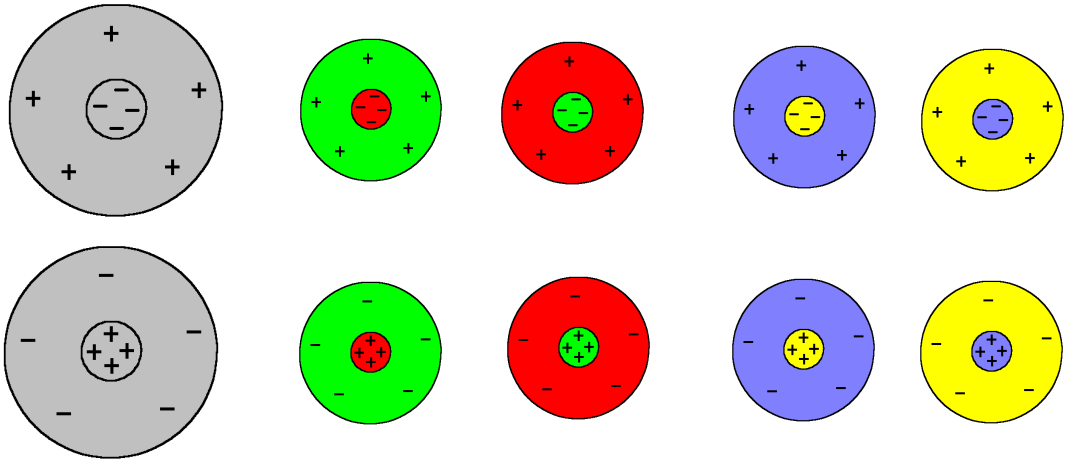

Figure 4.2. Retinal ganglion center surround receptive field types

(Left) M cells have larger receptive fields. (Right) P cells have smaller receptive fields and they are color sensitive. (Top) Center-off surround-on receptive fields (Bottom) Center-on surround-off receptive fields.

P cells are the most common cell type in the retina. They are sensitive to color. They can have red-green or yellow-blue receptive fields. Red green types can be further divided into red-center green-surround and green-center red-surround subtypes. Similarly there are also P cells having either yellow-center blue-surround or blue-center yellow-surround receptive field.

Receptive field size closely depends on the position of the ganglion cell. For example some ganglion cells on the fovea region receive input from only one photoreceptor cell (only cones), while some on the peripheral regions receive input from ten thousands of photoreceptors. This has some computational implications which will be later discussed[6].

[6]Since ganglion receptive fields represent band pass filters (see subsections 4.2.1 and 4.2.2 below) cells that have various receptive field sizes effectively allows sensitivity to various intervals of frequencies. This is relevant to the idea of multifrequency channels and the multiresolution scheme, discussed in sections 5.2 and 5.3 .

4.2.1 Mathematical Formulation

Receptive field of the retinal ganglion cells generally modeled using difference of Gaussians (this resembles Mexican Hat wavelets, see subsection 5.2.1) [7]:

$$O \sim \omega_c \exp[-k^2 \sigma_c^2/2] - \omega_s \exp[-k^2 \sigma_s^2/2] \qquad \text{(Equation 4.1)}$$

where output response O increases with k until a peak frequency k_p, then decreases symmetrically (Zhaoping, 2012, p.21).

Since the output response is most sensitive to an interval (or a band) of frequencies, one can conclude that *center-surround* type receptive fields of retinal ganglion cells such as P and M cells, mostly behave like a *band pass filter*.

4.2.2 Computational Properties

Center surround receptive fields, regular and precise connections and mosaic positioning of cells types have several computational advantages. Firstly, they result in band pass filters that *reduce the redundancies* and in effect compress the input data. This can also be predicted from the fact that the number of rod and cone cells are much higher (100x) than ganglion cells (Curcio et al., 1990). Secondly, retina, consisting of several types of neurons, intrinsically has some *nonlinear* properties. This nonlinearity results in high degrees of *decorrelation*. That is, high contrast images can be coded (and transmitted through the optic nerve fiber bottleneck) with higher efficiencies (Pitkow et al., 2012). Thirdly in color vision, because wavelengths of red and green color are very close, ganglion cell types having red-center, green-surround receptive fields or cells having green-center, red surround receptive fields enhance the difference between them. In addition to this, receptive field mosaics, (a uniform *spatial* arrangement of similar cell types with similar receptive fields), produce a *uniform sampling* mechanism of visual space (Anishchenko *et al.*, 2010). Moreover, average response is kept mostly constant in natural scenes, independent from receptive field size of

[7] Derivation of the formula is given in the Appendix.

ganglion cells (Graham et al., 2006). Therefore, these points show that intrinsic nonlinearity and receptive field properties of various cell types in the retina, transform the input into a more “whitened” or flattened and balanced form through decorrelation, via a well organized work from ganglion cells with different receptive field types.

There are also some trade-offs. For instance, retina is dominated by the rod type photoreceptors. Moreover, with increased distance from fovea, ganglion cells receive input from more and more rod cells. This effectively create larger receptive fields and higher sensitivity to light at the cost of higher precision. To achieve high resolution in a compensatory way, cone receptors are crowded together into a focused area called fovea. However, this in turn makes it necessary for the eyes to make saccadic movements, jump from one spot to another to “bring the objects of interests to the fovea” (Zhaoping, 2012, p.24) Also, unlike some invertebrates such as mollusks, all vertebrates have a blind spot because of the inverse order of layers where the optic nerve has to pass through retina (Lamb, 2011). As a consequence, human visual system uses *spatial sampling* to fill in the “blanks”.

4.3 LGN and Primary Visual Cortex

Optic nerve, which is considered as an information bottleneck, carries the activation information of retinal ganglion cells to lateral geniculate neuclei (LGN) which is a subregion of thalamus. LGN cells then transmit the information to (mostly) primary visual cortex. LGN has several roles and in addition to connections from the retinal ganglion cells, its cells also receive a high amount of feedback from higher visual areas. For now, only the feed forward connections and the role of LGN cells from the traditional perspective will be discussed.

Primary visual cortex (V1) is the largest area in the occipital lobe (or visual cortex). *Optic radiations* from LGN create the receptive field structures of two major cell types called *simple* and *complex* cells (Hubel & Wiesel, 1962). Simple cells generally have excitatory and inhibitory

regions in their receptive fields. They are mostly classified as edge or bar detectors; they are also sensitive to orientation. Complex cells are more common than simple cells. Generally they have large receptive fields and they can respond to moving lines or edges in an orientation and direction specific way. However, their receptive fields in general are harder to model and have nonlinear characteristics (such as lack of sensitivity to small spatial shifts).

4.3.1 Mathematical Formulation

At higher levels, the transformation of the visual input results in more complex spatio-temporal receptive fields. Since the connection scheme is much more complex than the retina, receptive field models are not directly derived from the circuitry; instead, a proposed mathematical model is directly compared to the receptive field of the relevant cell type(s) in the higher levels of the visual system, to see how much the mathematical model fits the biological data (i.e. Young & Lesperance, 2001). Below, some of these mathematical models are discussed.

Lateral Geniculate Nucleus (LGN)

Like retinal ganglion cells, LGN cells have center-surround receptive fields. LGN cells in layers 1 and 2 resemble magnocellular cells and in layers 3 to 6 they resemble parvocellular cells. Since they bear similarities to retinal ganglion cells, their spatial filters[8] are mostly modeled as a difference of Gaussians as in Equation 4.1. However, there are also models where LGN cells are assumed to have small orientation biases that later can lead to a "*sharpening*" of orientation selectivity in visual cortex (Kuhlmann & Vidyasagar, 2011). Kuhlmann et al. model their spatial filter as below

$$K_{xy}(x,y) = A\exp\left[\frac{x^2}{c_h^2} + \frac{y^2}{c_v^2}\right] - B\exp\left[\frac{x^2}{s_h^2} + \frac{y^2}{s_v^2}\right] \qquad \text{(Equation 4.2)}$$

[8]Spatio-temporal filters are often called kernel functions. See Appendix for more information.

where the constants A, B and c_h, c_v and s_h,s_v are used to define horizontal, vertical and center characteristics of inner and outer Gaussians. To introduce an orientation bias in a generic way, the modeler can first define a K_{xy} with a vertically or horizontally biased anisotropic center and then rotate it (Kuhlmann et al., 2011).

Unlike retinal ganglion cells, LGN cells also act like transient filters in time (Teich & Qian, 2006). That is, in a sense, they compute the f*irst order temporal derivative* of the visual stimuli[9]. Temporal filter K_t for LGN cells şs defined as

$$K_t(t) = \frac{t}{\tau^2}\exp\left(\frac{-t}{\tau}\right)\cos(\omega_t t + \varphi) \qquad \text{(Equation 4.3)}$$

where τ is response time constant (or "the duration of the temporal envelope"), ω_t is the temporal frequency for the sinusoidal term to generate excitatory or inhibitory responses, and φ is the temporal phase (Kuhlmann et al., 2011, Teich et al., 2006).

Overall, assuming an input stimulus S(x,y,t), the response of LGN cells O_{LGN} can be formulated as the spatio-temporal convolutions of S with the space-time separable $K(x,y,t) = K_t(t)K_{xy}(x,y)$ as below (Teich & Qian, 2006).

$$O_{LGN} = S(x,y,t) * K_t(t) * K_{xy}(x,y) \qquad \text{(Equation 4.4)}$$

Above formulation can be used in feed forward linear models. However, in reality, the circuitry in LGN is more complex. For example, there are koniocelluler cells (which do not have center surround receptive field) in addition to magnocellular and parvocellular cells (Saalmann & Kastner, 2009). Moreover there are nonlinear components due to the feedback form visual cortex as well as nonlinearity directly from retina. Therefore in a more realistic model, one may need to take into account feedback and nonlinearity.

[9]Some may also define LGN receptive field as Laplacian of a Gaussian (for spatial domain) multiplied by the *first order time derivative* of a Gaussian.

Primary Visual Cortex

Primary visual cortex has several computational properties. It has different cell types with different mathematical properties, as well as a well organized connection scheme which results in retinotopic map as discussed below.

Retinotopic Map

In the primary visual cortex, number of neurons is much higher (100x) than the ganglion cells in the retina (Zhaoping, 2012). Yet, neighborhood information within the image is mostly preserved in V1 and also V2, V3 and V4, even though the visual input is filtered and preprocessed during its transformation to the cortical surface. That is, from retina to visual cortex, activity within close by regions still maintains a spatial relationship (Wu *et al.*, 2012). However, similar to the increased number of ganglion cells and photoreceptors in fovea, the number of neurons dedicated to central vision is proportionally high in the visual cortex (around half of the total number of neurons in visual cortex). There is also distortion in the angles. Thus, spatial relationship is not straightforward[10].

Simple and Complex Cells

Primary visual cortex contains several types of cells which are in the traditional model simplified into two general types: complex and simple cells. Below, some mathematical models for both cell types are discussed.

Simple Cells

Simple cells in the early visual system have receptive fields that can be classified as Gaussian derivatives (Young & Lesperance, 2001). Gaussian derivatives in general also act like *band pass* filters. Moreover they closely resemble to Gabor functions (where a sinusoidal is multiplied with a Gaussian function). In fact, the limiting case for the higher order derivatives of a Gaussian leads to a Gabor function. It appears, in certain

[10]See the Appendix for mathematical formulation.

cases, Gaussian derivatives fit to experimental data even better than Gabor functions (Young et al., 2001). Thus, for simple cells, Gaussian Derivative (GD) spatio-temporal model will be discussed.

If a Gaussian basis function g_0 is defined as,

$$g_0(x)=e^{-x^2/2} \quad \text{(Equation 4.5)}$$

then derivatives of g_0 which are

$$g_n(x)=\frac{d^n}{dx^n}g_0(x) \quad \textit{for n=1,2,3...} \quad \text{(Equation 4.6)}$$

can be used in the representation of a receptive field. To exemplify, for a single dimension, a receptive field can be modeled using Gaussian derivatives such as

$$g_1(x)=-x\,g_0(x) \quad \text{(Equation 4.7)}$$

$$g_2(x)=(x^2-1)\,g_0(x) \quad \text{(Equation 4.8)}$$

$$g_3(x)=-(x^3-3x)\,g_0(x) \quad \text{(Equation 4.9)}$$

$$g_4(x)=(x^4-6x^2+3)\,g_0(x) \quad \text{(Equation 4.10)}$$

where n is 1,2,3 and 4. As one may observe, the derivative of a Gaussian is simply a multiplication with a polynomial of the same degree (i.e. 4th derivative means multiplication of basis with a polynomial with degree 4). Therefore, instead of a multiplication with a sinusoidal as in the case of Gabor functions, GD spatio-temporal model uses a polynomial.

The generic formula for the real GD basis function is

$$G_{n,o,p}(x',y',t')=g_n(x')g_o(y')g_p(t') \quad \textit{for n,o,p = 0,1,2,...} \quad \text{(Equation 4.11)}$$

the multiplication of three one-dimensional Gaussian derivatives, where x',y',t' are normalized coordinate axes and n,o,p are order of derivative for the coordinate axes respectively.

A simplified version of the above formula that still fits the experimental data is also given

$$G_{n,p}(x',y',t')=g_n(x')g_0(y')g_p(t') \quad \textit{for n=0,1,2,3,4, p=0,1} \quad \text{(Equation 4.12)}$$

where o is no longer necessary (Young et al., 2001).

A discrete version of the above model, which is biologically more relevant is called Difference of Offset-Gaussians (DOOG) (Young *et al.*, 2001). Since a derivative is the limit of the difference approaching zero, derivatives for the one dimensional case are

$$g_1(x) = g_0(x+h) - g_0(x-h) \quad \text{(Equation 4.13)}$$

$$g_2(x) = g_0(x+2h) - 2g_0(x) + g(x-2h) \quad \text{(Equation 4.14)}$$

$$g_3(x) = g_0(x+3h) - 3g_0(x+h) + 3g_0(x-h) - g(x-3h) \quad \text{(Equation 4.15)}$$

$$g_3(x) = g_0(x+4h) - 4g_0(x+2h) + 6g_0(x) - 4g(x-2h) + g(x-4h) \quad \text{(Equation 4.16)}$$

where h goes to zero. The above weights correspond to a Pascal triangle

1

1 -1

1 -2 1

1 -3 3 -1

1 -4 6 -4 1

They can be predicted by a “function of distance” from the middle of a random normal distribution (Young *et al.*, 2001). The signs are interpreted as a mixing of inhibitory and excitatory inputs. It is biologically plausible that Gaussian-like connections are constructed by a connection scheme in which the probability of connections decreases with distance, also reducing the wiring cost[11]. Moreover, because g_n can be constructed by g_{n-1} and g_{n-1} can be constructed by g_{n-2} and so on, they may also offer a biologically plausible model for the sequential processing of the visual input.

Even though GD spatio-temporal model and its discrete version DOOG explain some biological phenomena, they are linear models and they fail to explain nonlinear events. Especially for complex cells, GD model

[11]This idea (Gaussian like connection scheme that depends on distance) is used in the computer model discussed in chapter 6.

requires nonlinear components. Therefore, below, a nonlinear model for complex cells which is inspired from GD model is given.

Complex Cells

Complex cells are not as well understood as simple cells. While their temporal response is similar to simple cells, they lack a well defined spatial receptive field. Below is a *simplified* formulation, based on GD model with a nonlinear characteristic[12]

$$C(x,\theta)=max_t\left|S(x)*G_1(x+\omega t,\theta)\right|,\ \ where\ \ |t|\leq p \tag{4.17}$$

where, x denotes a spatial vector $(x,y)^T$. S(x) is the original visual input and G_1 is the Gaussian kernel[13] rotated by the angle θ for orientation selectivity. After the rotation by angle θ, the model behaves as if there was a spatial axis where single cells are aligned. Note that as long as the shift magnitude |t| is smaller than p, response C will always return the maximum magnitude of the convolution of signal S and Gaussian kernel G_1. Thus, this model takes into account the insensitivities to the small spatial shifts observed in complex cells (Hansard & Horaud, 2011).

Since a nonlinear component is integrated, potentially, Hansard and Horaud's model can describe the receptive field of complex cells better than linear models. Moreover, since their model is based on GD model and as discussed in the previous subsection, GD model and its discrete version have biologically plausible properties, Hansard and Horaud's model may also incorporate biologically plausible properties. However, their model seems to be still “in development”, since there are certain problems such as p being too general, no scaling parameters for receptive fields, usage of the basis of only the first order etc. (Hansard et al., 2011). Yet, by adding nonlinearity to achieve a more realistic behavior, this model proclaims an incoming of models in the near future where complexity is embraced for the sake of expressive power and biological plausibility.

[12]Here, a nonlinear characteristic is achieved via conditional behavior. The output of the system is not always directly proportional to the input anymore.

[13]See the Appendix for more information on kernel functions.

4.3.2 Modern View

Gabor filter, DOOG and GD spatio-temporal models had a fair amount of success in explaining the early vision. These models and traditional hierarchical view of visual processing are closely connected. However these models generally show few cues on whether they are compatible with the modern view of the visual system.

There are various conceptual/computational perspectives which are incorporated into modern view of the visual system. For example, *efficient coding perspective* has an important role on the mathematical formulations of early vision (Pitkow & Meister, 2012). Since the optic nerve is considered as an information bottleneck, the efficient coding principle states that early vision must somehow maximally compress the visual signal, keeping as much relevant information as possible. To achieve that, an efficient encoding mechanism would remove the redundancies and transform the signal into a set of *uncorrelated data* which can still be used in a fairly efficient reconstruction or decoding phase. However this is not simply achieved via center-surround receptive fields of the retinal ganglion cells which was taken into account in the traditional models; Pitkow and Meister's research shows that efficient coding also heavily depends on the intrinsic *nonlinearity* in the retina which is largely ignored in the mathematical models.

There is also the more recent *V1 saliency map hypothesis* (Zhaoping, 2012). A bottom up saliency map may further refine the information selectivity, also serving as a bottom up filtering mechanism for *attention*. This alternative perspective to early vision can explain the redundancies which may still be present in the transformed visual input. Saliency map hypothesis also takes into account intra-cortical interactions and therefore it is a more modern view of the visual system (see The Modern View below). *Priority map hypothesis* builds upon the saliency map hypothesis. It states that there is always an attentional priority which behaves as a dynamical system (Bisley, 2011). Attentional priority is constructed dynamically by both bottom up (saliency map) and top down

drives (task goals, personal biases, evaluation of importance etc). According to this theory, the peak of attentional priority map changes dynamically according to the eye movements (which themselves are controlled by the attentional peak on the priority map).

A Comparison Between the Modern and Traditional View

In mammalian visual systems, there are at least twelve afferent channels (Masland et al., 2007, Rockhill *et al.*, 2002). Reciprocal feedback between cortical areas as well as cortical and thalamic regions is common. Moreover there is nonlinearity even at the retinal ganglion cell level (Schwartz et al., 2011, Pitkow et al., 2012). Therefore, traditional models make several simplifications when assuming a homogeneous sea of ganglion cell types having only canonical concentric center-surround receptive fields with prominently feed-forward connections and linear behavior (Martin & Solomon, 2011). A summary of the traditional and modern view is illustrated below in *Figure 4.3*. The traditional view is summarized in two main stages :

(A) Pathways: retinal ganglion cells (having center-surround receptive fields) transmit information in parallel via (MC) magnocellular (movement and distance) and (PC) parvocellular (color and find detail) pathways to LGN.

(B) Then in visual cortex, a line of adjacent LGN cells having center surround concentric receptive fields are used as feed forward inputs to a cortical neuron such as a simple or a complex cell to detect edge, orientation and/or movement; finally with increasing levels of feature selection, (A) visual input is further divided into where (position) and what (identity) pathways. In *Figure 4.3,* the modern view raises following criticisms to the traditional view:

(C) There are several parallel pathways or *channels* (more than a dozen), for example non-standard cells such as koniocellular cells (KC) also contribute to the vision via KC layers in LGN, superior colliculus (SC) and lateral posterior-pulvinar complex (LP).

(D) Feedback between cortical regions (cortico-cortical pathways) and from cortical regions to LP, SC and LGN (cortico-thalamic pathways) is fairly common. In fact at least half of the input to thalamus comes from visual cortex; feedback to primary visual cortex from other cortical regions is also common. The amount of retinal input to LGN is *as low as ten per cent* (Saalmann et al., 2009).

(E) Modern signal processing scheme in primary visual cortex takes into account the role of feedback and reciprocal connections between the neurons processing related parts of information within the spatio-temporal visual stimuli. Contrast resolution in LGN is increased via cortico-thalamic feedback. In general, recent evidence points to the role of high level perception and cognition in the modulation of LGN (Saalmann et al., 2009).

Overall, with recent findings, it is evident that traditional computational models that still assume a simple feed-forward visual system require refinements to achieve better biological plausibility. Modern view embraces a dynamical model with a lot of reciprocal feedback and parallel channels. Therefore, parallel channels should be taken into account. For example, receptive fields of retinal ganglion cells is essentially a band pass filter. Retinal ganglion cells have various receptive field sizes that depend on cell types and distance to the fovea. This allows selective sensitivity to various intervals of frequencies (i.e. *multifrequency channels*). Such selective sensitivity is important, because it is required when the visual system decomposes the stimulus into its constituents. This will be discussed in more detail in the next chapter (see subsections 5.1 to 5.3).

For simple cell types, Young et al.'s GD spatio-temporal model and its discrete version predict a hierarchy of cell types each having Gaussian like connection scheme that depends on distance (see subsection 4.3.1). Such a connection scheme also decreases the overall wiring cost, since long range connections are kept minimum. This idea is incorporated in the computer model discussed in chapter 6.

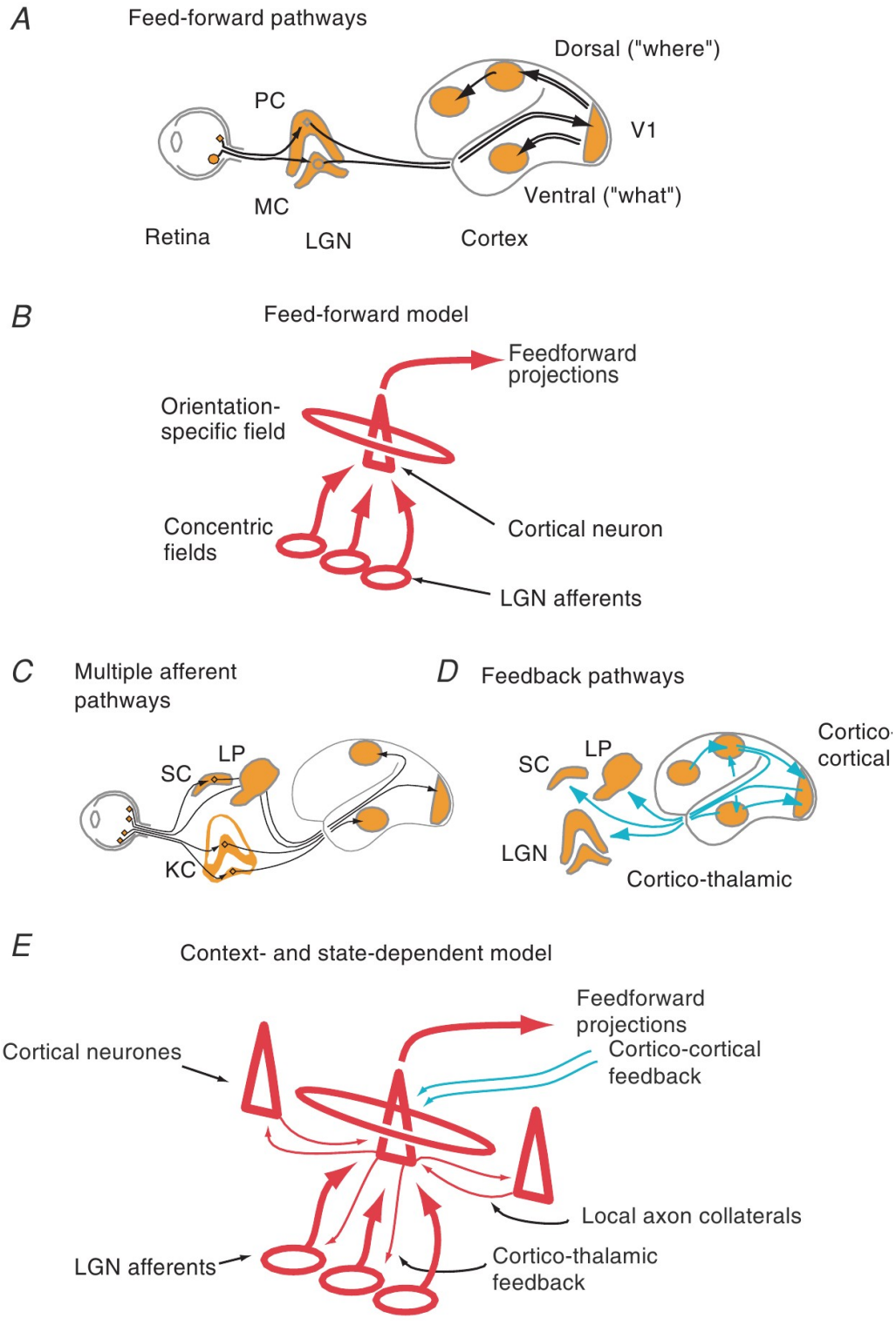

Figure 4.3. Recent additions to the traditional view

(A) and (B) depict the traditional view, (C), (D), (E) illustrate the contributions of modern view (Martin & Solomon, 2011, p.30).

CHAPTER 5

5 Synthesis

In the previous chapters, features of the visual system from evolutionary, developmental and computational perspectives were discussed. A subset of these explored features have underlying principles that are essential to the computational model developed in this thesis work. These “distilled principles” (and relevant information) will be discussed in this chapter.

The first principle is about controlling *entropy*, therefore precision and *resolution*. This is closely related to the information theory. A biological system that has *multi-scale resolution* (also possibly multi-scale organization) can minimize joint entropy. This will be discussed in sections 5.1 to 5.3.

The second principle is about evolution and *reusability*. A biological system that has a component which is mathematically or computationally meaningful, can maximize reusability. This will be discussed in section 5.4.

The third principle is about development and *edge of chaos*. Changing cell cycle in early development can have *chaotic* results. This will be discussed in section 5.5.

5.1 Precision and Joint Entropy

Transformation of visual signal can be investigated from the information theory perspective. Assuming orthogonal time and frequency domains[14], it is a well established phenomenon that there is a duality between their precision (Lewis & Mayer, 1929). Increase of precision in one domain results in uncertainty in the other domain, therefore they are inversely related. The relationship between two domains is given by Gabor as the *joint entropy*

$$\Delta t \, \Delta f \geq \frac{1}{2} \tag{5.1}$$

where Δt and Δf are the entropy in time and frequency domain respectively (Gabor, 1946 as cited in Silveira et al., 2008). This states that simultaneous increase in the precision of both frequency and time domain is impossible.

Above inequality predicts an advantage of having receptive fields with variant time/frequency resolutions. If retinal ganglion cells were all *identical*, they would reduce the uncertainty (or entropy) in only one domain at the cost of losing all the precision in the other domain. Retina has more than a dozen channels that incorporate cell types that have complementary roles. Moreover, receptive field size of each cell type can be variant.

Therefore, this brings an information theoretic explanation to the phenomena such as receptive fields of retinal ganglion cells narrowing down in fovea and spreading out in peripheral regions and also different retinal ganglion cell types having different spatial resolution. *This is necessary to take advantage of variant precision in time and frequency domains.* Moreover receptive field of ganglions are also almost optimal, since they are very similar to Gabor functions which have *minimal joint entropy* (see the next subsection).

[14] In the traditional sense, time domain represents the domain *where the raw input or signal is*. The raw input is can be a function of space (spatial input), or a function of time (temporal input). Frequency domain represents the domain of *transformed signal*. For example it can be temporal or spatial frequency domain.

5.1.1 Gabor functions

Gabor functions have minimal joint entropy in time and frequency domains (5.1) (Gabor, 1946). A Gabor function is in essence a harmonic oscillation multiplied by a Gaussian. General formula is given by

$$\psi(t)=\exp[-\alpha^2(t-t_0)^2]\exp[2\pi i f_0(t-t_0)+\theta i] \quad (5.2)$$

where f_0 controls oscillation frequency, θ is phase, α and t_0 control sharpness and peak (Silveira et al.., 2008).

Transformation of a Gabor function between reciprocal domains (time&frequency) using Fourier transform gives the same “analytical form” (Silveira, et al., 2008). Fourier transform of Gabor function is

$$\varphi(f)=\int \psi(t)e^{-2\pi ift}dt \quad (5.3)$$

$$\varphi(f)=\exp[-(\frac{\pi}{\alpha})^2(f-f_0)^2]\exp[2\pi i(f_0-f)+\theta i] \quad (5.4)$$

Gabor functions can be used as basis functions in *expansion of other functions*. Therefore any function can be represented by Gabor functions or Gabor “atoms”.

5.1.2 P and M Receptive Fields

Receptive field of Parvocellular (P) and magnocellular (M) cells “fit together”. They fit together (*within* the cell types) as each cell type can have either center-on or center-off receptive fields. It turns out this can be explained in terms of function expansions. That is, P and M cells may be operators of some form of mathematical expansion of visual input that uses Gabor atoms as basis functions (Silveira et al., 2008).

Moreover, their receptive fields are complementary (*between* the cell types). While M cells have high precision in 1D time and 2D spatial frequency domain, they have low resolution in 2D space domain and 1D temporal frequency domain. Conversely, while P cells have high precision on 2D space domain and 1D temporal frequency domain and they have

low precision on the reciprocal domains[15] (Silveira et al., 2008). High temporal and spatial resolution, as one may observe, cannot be achieved together. This also explains why P and M pathways specialized into parallel or *multifrequency* channels.

5.2 Multiresolution Analysis and Wavelet Transform

Wavelet transform is defined by Mallat as the "decomposition into a set of *frequency channels*, having the same bandwidth on a logaritmic scale" (Mallat, 1989b, p.2091). (See the relation with early vision above in 5.1.2. and below in 5.3)

With Fourier transform, a function (which essentially has perfect precision in the time domain) is transformed into another function that acquires perfect precision in the frequency domain. However, it loses all the precision in the time domain. To prevent this, short-time Fourier transform (STFT) can be used. A time window of constant size is necessary to achieve locality in both time and frequency domains. However, adjusting the size of the time window should be done manually.

The main motivation of multiresolution analysis is that, natural visual stimuli consist of objects having different sizes. Large objects do not require high resolution and small objects do not require low resolution. Since there is no *a priori* information on the size of objects, with STFT, adjusting the time window according to each image is required for better performance. To prevent this, multifrequency channel decomposition is used, where time window is not constant but changing. This also achieves a *time-frequency representation*, intrinsically keeping some precision from both time and frequency domains. Below, wavelets and multiresolution analysis are described in more detail.

[15]Note that the traditional "time domain" (which has an entropy Δt) represents here 2D space and 1D time, while "frequency domain" (which has an entropy Δf) represents 2D spatial frequency and 1D temporal frequency.

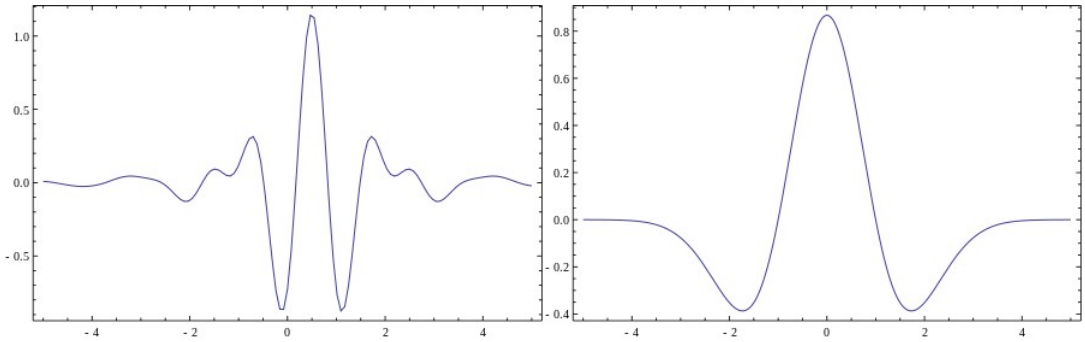

Figure 5.1. Wavelets

(Left) Meyer Wavelet, (Right) Mexican Hat Wavelet

(From "Meyer Wavelet" by J.M. Loone, 2012, http://en.wikipedia.org/wiki/File:MeyerMathematica.svg. Copyright 2012 by Jon Mac Loone, From "Mexican Hat Wavelet" by J.M. Loone,2012, http://en.wikipedia.org/wiki/File:MexicanHatMathematica.svg,Copyright 2012 by Jon Mac Loone. Reprinted with permission.)

5.2.1 Wavelets

Wavelets are localized forms of waves which integrate to zero (Figure 5.1). They are used in areas such as image compression, i.e. digital fingerprint image compression by FBI. Also, wavelet decomposition / *thresholding* / composition strategy on raw data can greatly improve the data quality, getting rid of the *noise*.

Wavelets can be used as basis functions to represent any function (similar to sines and cosines used as basis functions in Fourier analysis). "Mother wavelet"s can be dilated and shifted (translated) to create specialized variants which can be derived from below.

$$\psi_{jk}(x) = c\,\psi(2^j x - k) \tag{5.5}$$

These variants can create a basis for $L^2(R)$, where c is a constant, and L^2 is the Hilbert space of functions that have finite energy (functions that are square integrable). That is, any square integrable function can be represented by the linear combinations of ψ_{jk}. Simplest and oldest example of wavelets is called Haar wavelet (Block, Rogers & Ruck, 1994).

It is a simple step function, defined between [0,1]. Dilation and translation operations are illustrated in Figure 5.2.

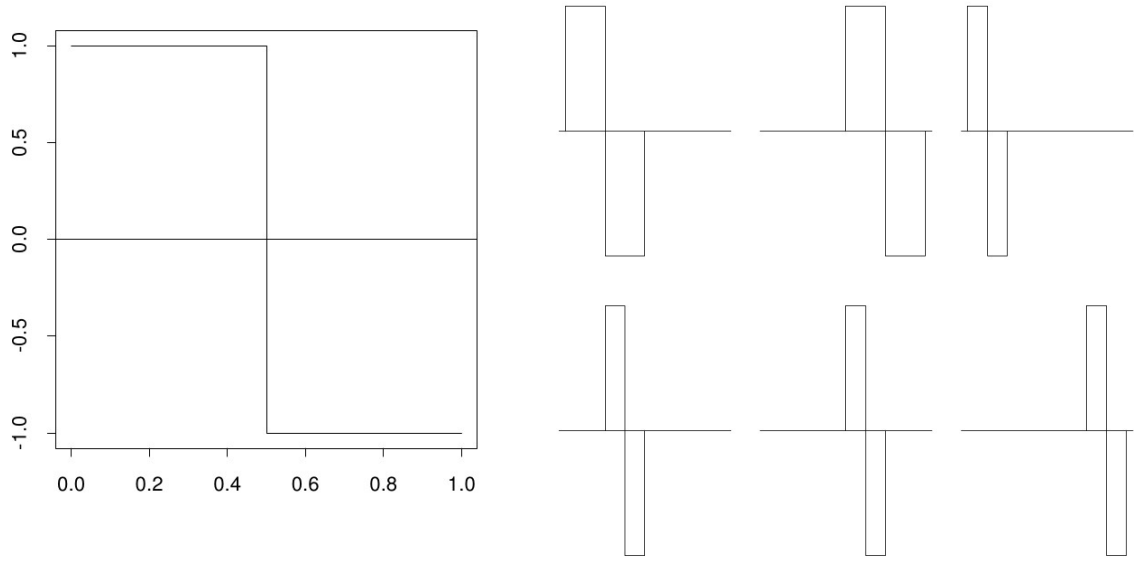

Figure 5.2. Haar wavelets

(Left) Mother Haar wavelet (Right) Scaled and shifted versions, their linear combinations can represent any square integrable function

5.2.2 DWT and Multiresolution Analysis

Discrete wavelet transform (DWT) and multiresolution analysis (MRA) intrinsically make use of the information theoretic ideas described in section 5.1. Unlike Fourier transform, wavelet transforms take advantage of wavelet functions that are local in *both time and space* (Mallat, 1989a).

Multiresolution analysis, which unifies the earlier methods such as “subband coding” and “pyramidal coding”, analyzes the signal in different resolutions. This is achieved via *upsampling* and *subsampling* where the rate of sampling is increased or decreased by a factor of 2. Scale of the signal is doubled whenever there is low pass filter (and subsampling) and it is halved whenever there is high pass filter (and upsampling). This is done in a hierarchical way, effectively dividing signal

into “multifrequency channels” and creating an analysis of the signal consisting of several components that have different precision in time and frequency domains (Mallat, 1989b).

As the first step, DWT decomposes the signal into its coarse (low frequency) and detailed (high frequency) components. Then, DWT *recursively repeats* the same operation on the high frequency component. Each step of decomposition can be described as below:

$$X_h[k] = \sum_n x[n] g[2k - n] \tag{5.7}$$

$$X_l[k] = \sum_n x[n] h[2k - n] \tag{5.8}$$

where X_h is the high frequency component X_l is the low frequency component, filtered by g (high pass filter) and h (low pass filter). At each step, time resolution is halved and frequency resolution is doubled.

5.3 Early Visual Processing and Multiresolution Analysis

When introducing the multiresolution analysis to the scientific community, Stephane Mallat and Yves Meyer were already aware of the fact that early visual processing has “multifrequency channels”. From Mallat's own words:

> ..[M]ultichannel models have been particularly successful in explaining some low-level processing in the visual cortex. The expansion of a function into several frequency channels provides representation which is intermediate between a spatial and a Fourier representation. ...*Biological studies of human vision have always been a source of ideas* for computer vision and image processing research. Indeed the human visiual system is generally considered to be an optimal image processor. (Mallat, 1989b, p.2091)

Application of this idea which was inspired from biology, to image processing was a success. Their ideas were fairly well received by the image processing community. In fact, most of their ideas later became part of the JPEG2000 standard (Unser & Blu, 2003).

Multiresolution scheme was also used in image compression methods such as image pyramids. Image pyramid structure closely resembles to human visual encoding. Pyramid algorithms use spatial orientations in a similar manner to the human visual system (Wandell, 1995).

5.3.1 Evolution and Multiresolution Scheme

A robust perception system requires a mechanism to analyze all relevant types of natural stimuli. How can this be achieved in a generic way? The answer is decomposition of the input into its "constituents". In the case of visual processing, creating a time-frequency representation of the visual signal has evolutionary advantages for predatory behavior, mate detection, recognition of moving objects etc. How does the visual system decompose the signal into its constituents? Theoretically this can be achieved via Fourier (uses pure frequency representation, no locality) or more plausibly, wavelet analysis (has locality, this intrinsically keeps some time representation as well).

Note that the decomposition method may not be necessarily universal among animals; the only necessity is a generic method to analyze aspects of natural visual stimuli that is relevant to the organism. However, in any case, this brings the time-frequency duality into the scene. That is, the more precision the organism acquires in perceiving the stimuli (time representation), the less precise the analytic representation of the stimuli (frequency representation) becomes.

Evolution of Parallel Channels

Researchers in the image processing community (i.e. Mallat 1989b, Wandell, 1995) already suspect that a biological correlate to multiresolution scheme exist in the visual system. Assuming that the most primitive visual system had identical ganglion types, why multiple channels had evolved? Silveria et al. (2008) propose an information theoretical reason (namely joint entropy) for the existence of multi-frequency channels (P and M pathways) in the visual system. As

discussed above and in section 5.1, joint entropy prevents the evolution of a single visual pathway with identical cells that has both high time and high frequency resolution[16].

Evolution of an organism that has a single visual pathway specialized for temporal resolution can be possible. However, high temporal precision would result in low precision in the domain of temporal *frequency*, (therefore ambiguous temporal “constituents“ to analyze the signal). Evolution of an organism that is good at resolving the spatial details is also possible, yet the same problem appears, this time in the spatial frequency domain. Thus, for a balanced perception, evolution of complementary parallel channels at some point is a necessity. Meanwhile, Gabor function like receptive fields which minimize joint entropy can also evolve; however, even with such receptive fields, without parallel channels or variant receptive field size, no more improvements can be achieved.

A multiscale analyisis, or in a more generalized sense, a multiresolution scheme may provide a solution to the problem stated above, since a multiresolution scheme would allow a balanced representation of time and frequency domains. That is, *to acquire complementary information on time-frequency representation that has variant time/frequency precision ratios (or to work around the joint entropy problem), emergence of a multiresolution scheme may have been necessary for the evolution of a robust visual system*. Note that instead of the term multiresolution analysis, the term multiresolution scheme is used. This is because evolution can find various solutions to the same problem. The only requirement is to find a generic and balanced method to analyze the components of the signal *relevant to the organism*. This generic method may have nonlinearities. However, this does not cause a problem because there are examples of nonlinear multiresolution schemes such as nonlinear pyramid decomposition (Goutsias & Heijmans, 2000). Therefore, there is no reason for some form of multiresolution scheme to

[16]This is *impossible* because they represent reciprocal domains, therefore a transformation from one domain to another would result in precision loss.

be not used in the visual system to generate variant precision ratios in the reciprocal domains.

Where and What Pathways

What if above idea[17] also applies to higher levels in the visual cortex? One speculation would be that joint entropy principle brings an information theoretic explanation to where and what pathways. What and where pathways extract "mostly" independent features (where = a position in a map, object details is less precise, what = object details, object position is less precise) which can be considered as features of different dimensions. It may also be the case that they also complement each other in the reciprocal domains .

Supporting evidence for this claim may be found in the neuro-anatomical connections suggesting that parvocellular channel mainly feeds the ventral stream which is the what pathway. However, this does not mean that the ventral pathway is a continuation of P channels. Rather this simply should be seen as an evidence for a *biased* input that is more precise in one domain. The "*raw input*" coming to what pathway is probably already analyzed and transformed, yet it is still highly plausible that there is a bias and certain orthogonal features have "*highlighted*" precision while other features have low precision. It is also possible that, input to the where pathway has some of the exact opposite features highlighted. Therefore they may have, to some extent, complementary roles, from the joint entropy perspective.

Note that heavy connections between where and what pathways and resulting complex interactions should also be taken into account (Keizer et al., 2008). However, this requires a detailed investigation of high level processes in brain, which is outside the scope of this thesis.

[17] As explained in the previous subsection, a multiresolution scheme in the visual system is suspected/predicted by the image processing community. Combining this with the work of Silveira et al. (2008) (i.e. P and M segregation and joint entropy), it becomes evident that multiresolution scheme may be relevant in the biological context as an evolutionary solution to robustly work around the joint entropy problem.

5.4 Evolution and Reusability

A component that has mathematical/computational/abstract properties has a prominent advantage that can be summarized as reusability. The idea of reusability can be used to create a complex model from simple rules. A component in a model can be in essence, an abstraction of many possible components. (For instance a component that can become of immediate use in new contexts) Similarly, it can also be a multi-purpose component that already has several simultaneous roles.

To give an example from the visual system, center surround receptive fields have *several* usages such as filtering and removing redundancies and decorrelation of the input (subsection 4.2.2). Receptive fields also resemble Gabor function, which has the property of minimal joint entropy discussed in section 5.1. Ganglion cell receptive fields have varying sizes and, in a sense, they are parameterized according to the distance from fovea. Mosaic receptive field structures for the same ganglion types along the retina and uniform sampling of the visual input is also related, therefore this organization requires an elaborate organization of "reusable components". Multiresolution scheme also intrinsically has reusability (reuses the mother wavelet). Moreover, *image blending* task, which visual system has to do constantly, can be achieved via a multiresolution scheme (Burt & Adelson, 1983, Wandell, 1995).

From the evolutionary perspective, since the advantages of reusable components are many, one may expect complex organisms to acquire several reusable components. Moreover, because evolution of complex organs requires mechanisms such as exaptation (section 2.3), having an "abstract" component that can be used in several contexts would promote the increase of complexity via exaptation. As the toolbox of reusable components enlarges, combinatorial usage would be more plausible. As discussed section in 2.4, novelties are indeed in the form of new combinatorial usages and small changes.

From the developmental perspective, specific combinations of reusable components translate to specialized or differentiated cell behavior. For

example same genes can be used in both neurulation and then later in axon guidance (subsection 3.1.2). A more extensive research shows that “a surprisingly small number of signaling pathways are used reiteratively during neural development, eliciting very different responses depending on the cellular context” (Kiecker & Lumsden, 2009). In fact, the more ancient the component, the better tested it becomes, and many functionalities depends on these ancient components. Because with evolution an increasing number of functionalities become dependent on reusable components, these components, as well as the systems that are build upon them, become harder to change with time. This may be a rule of thumb for any system that successively increase its complexity. This idea is also applicable to the circuitry of the brain, evolution of gene regulatory networks and even the construction of roads, power grids or the development of the Internet. The resulting structure has often a characteristic form which is called a *scale free network* as illustrated below in Figure 5.3.

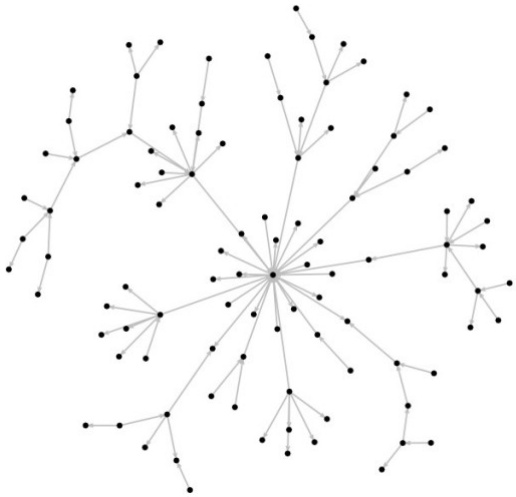

Figure 5.3. A gene regulatory network[18] (model)

Hub like nodes describe high amount of reusability and control, while nodes with few connections describe highly context specific usage. (Fujita *et al.*, 2007, p.41)

[18] *Genes* are hereditary molecular units which encode cell behavior, cell differentiation and cell growth. Transcription, translation, RNA processing and epigenetic mechanisms regulate gene behavior. These mechanisms generally trigger or inhibit other mechanisms and the overall system can be represented as a sparsely connected network, namely a *gene regulatory network*. Such a network is responsible from complex cell behavior.

5.4.1 Scale Free and Small World Networks

A scale free network is characterized by that the number of connections display a power law distribution (Barabasi & Albert, 1999). A scale free network can be constructed via addition of new nodes that have an increasing connection bias towards the nodes with higher number of connections. The probability to connect a node i is given by:

$$P_{conect}(i)=\frac{ck_i}{\sum k_j} \tag{5.9}$$

where k_i is the number of connections node i has and c is a constant.

Another way to construct such networks is using a *fitness model*. Each node has a fitness value and fitter nodes attract more nodes, while less fit nodes lose connections. Fitness values may vary from the start, thus the network topology may also change in a more dynamical way with the addition of each new node.

A critical property of scale free networks should be emphasized. *Random* node deletion generally does not have large effects on the topology (Barabasi & Albert, 1999). This explains the graceful degradation phenomenon and the robustness of gene regulatory networks to random mutations.

Small World Network

Another relevant network type that is commonly observed is *small world networks*. A small world network has the property that any node can be linked together via a small number of steps. Minimal wiring becomes a constraint as the brain size increases, therefore brain circuitry has the small world property. For example, laminar structures in the cortex minimizes connection lengths[19]. Moreover, brain has a network structure that can be defined as *clusters of clusters*. There are hub like regions which have a large number of incoming and outgoing connections as well as hub like neurons that connect to significantly more number of other

[19]Advantages of a laminar structure to reduce wiring cost were explored in the computer model in the next chapter using evolutionary algorithms.

pre-synaptic and post-synaptic neurons. Therefore connections in the brain are organized into a *hierarchy*, “from the microscopic cellular level via the mesoscopic level of local neural circuits and columns to the macroscopic level of nerve fiber projections between brain areas” (Zhou *et al.*, 2006). Overall, brain circuitry achieves scale free network and small world network properties via laminar stratification and a topology that resembles a *self repeating* structure, a fractal.

5.4.2 Fractals and Iterated Function Systems

Fractals can be generated using iterated function systems. Iterated function systems (IFS) are especially relevant, because they are local operators (on *contractive maps*) that transform a previous structure in a recursive way into a self symmetric structure, as illustrated below.

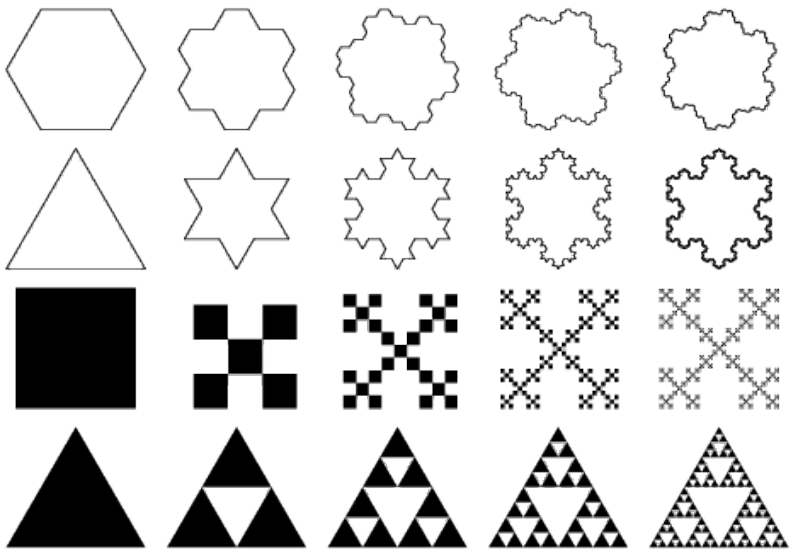

Figure 5.4. Iterated function system

Applying an iterated function system to a simple initial structure results in a more elaborate self-similar structure called fractals. Above, well known fractals such as Gosper island, Koch snowflake, box fractal and Sierpinski triangle are illustrated.

(From “Fractal” by E. Weisstein, 2012, http://mathworld.wolfram.com/Fractal.html. Copyright 2012 by E. Weisstein. Reprinted with permission.)

How is self similarity achieved in a developing organism? Theoretically a multi-agent system can create self similarity at *both behavioral and structural levels* (Hoskins, 1995). Therefore, developmental rules and cellular level interactions are capable of leading to an emergence of functional/ behavioral self similarity. Emergence of self similarity in a multi-agent system is relevant, because this means a set of local/developmental rules can create almost any hierarchical structure (i.e. a model of early visual system that uses multiresolution scheme, a network topology that displays a hierarchical organization similar to the brain, that is, a cluster of clusters). Also note that, unlike traditional IFS, local/developmental rules can create more than fractals. Combination of local rules that are used in a cell, can even change via differentiation.

Overall, the idea of reusable local rules is plausible. Combinations of local rules can be used for creating hierarchies and self similar structures (and in theory self similar behavior as well). Simple developmental local rules and differentiation can lead to creation of complex systems.

5.5 Development and Timing of Events

A disturbance in the timing of cell cycles of progenitor cells can have *chaotic* results. For example, according to Cecconi et al. (2007), a defect in apoptosis or cell cycle regulation of a small number of cells in the neural folds at the early stages of development can later affect large territories of the neural tube. Another example is that cell sizes can be affected from metabolic inputs. If the metabolic input is not controlled, increased cell size can disrupt the timing of cell cycle, this in turn can change the rate of proliferation and at the later phases of the development, this can be magnified into a large defect in the embryo. Therefore, small changes in the initial conditions, can later have large consequences. However, there is also robustness enough to produce “almost” the same phenotype from the same genotype (identical twins). Identical twins may have small differences in their brain anatomy or fingerprints (discussed in 3.5), yet they are proofs of high precision and

strong control of development. This somewhat chaotic strong control brings to the mind the notion called *edge of chaos* (Kauffman, 1993).

Strange Attractors

In a dynamical system, state changes or trajectories can be represented in phase space. If a system has nonlinearities, sometimes its phase space contains limit cycles. Limit cycles can be stable or unstable. If a limit cycle is stable, it is an *attractor*. That is, any neighboring trajectory will eventually converge to it. Therefore, the dynamical system eventually converges to a repetitive oscillatory behavior (Kauffman, 1993).

Strange attractors, on the other hand, are very different from stable limit cycles. They have properties that make them relevant for the development of complex organisms. They are unstable and mostly chaotic. Therefore, two neighboring trajectories that are on a strange attractor generally diverge and get arbitrarily far apart (Kauffman, 1993). However, obviously they cannot escape from the attractor. Moreover strange attractors have low dimensionality even in high dimensional state spaces. Therefore, this is literally “chaos in a box”.

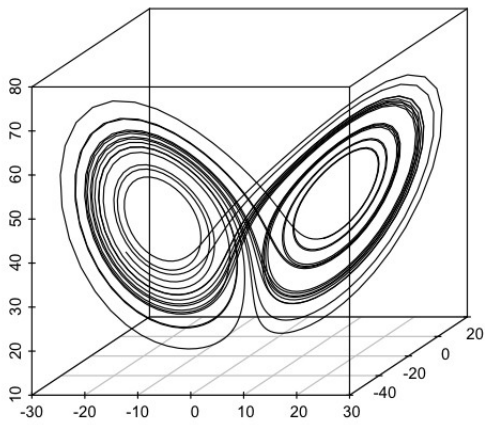

Figure 5.5. Lorenz attractor

(From “Lorenz attractor”, by S. Roberts, 2011, http://replicatedtypo.com/creative-cultural-transmission-as-chaotic-sampling/3684.html. Copyright 2011 by S. Roberts,Reprinted with permission)

Another critical idea from Kauffman is that since a dynamical system may have many parameters, by representing these parameters similarly in a parameter space, it is theoretically possible to describe developmental phenomena such as morphogenesis (Kauffman, 1993). This explains how large morphological differences can occur with small genetic differences (i.e. high morphological diversity between the species that are closely related, such as species on the same family).

Overall, as Kauffman (1993) stated, *edge of chaos* can be a diversification mechanism for the development. In its phase space, a gene regulatory network (which is essentially a dynamical system) can contain stable attractors. For example stable cell types and homeostatic mechanisms may correspond to stable attractors. There can also be unstable attractors. For instance cellular differentiation mechanisms and morphogenesis may correspond to unstable attractors. Both stable attractors and unstable attractors emerge from the interaction of the components of the gene regulatory network. Consequently, this can explain the curious phenomenon: “a surprisingly small number of signaling pathways are used reiteratively during neural development, eliciting very different responses depending on the cellular context” (Kiecker & Lumsden, 2009). This is because, simple interactions between a small number of (reusable) components have rich consequences.

5.6 Summary and Discussion

The investigation of visual system from various perspectives in the previous chapters revealed a core subset of evolutionary/developmental and conceptual/computational features that have underlying principles which are closely relevant to *information theory, network theory and dynamical systems theory*.

In the sections 5.1-5.3, the restrictive role of (joint) entropy on the evolution of parallel visual pathways and its relation to the multiresolution scheme were discussed. Also as a speculation, possible role of joint entropy on the segregation of where and what pathways

were mentioned. This may stimulate more information theoretic research on the role of joint entropy as an evolutionary constraint for the segregation of sensory pathways (and possibly higher brain regions).

In section 5.4, the idea that a developing/evolving complex system would need to successively build upon its simpler versions and the connection of this phenomenon to the idea of reusability were discussed. Having abstract or computationally meaningful components may be an evolutionary advantage because they maximize reusability. Thus, computationally meaningful structures may be more common in the complex organisms than one may predict. This may (partly) bring an evolutionary explanation to questions such as why does the visual system have highly precise structural components which are often associated with several computational characteristics.

As a structural counterpart to the reusability idea, the emergent structure which is often observed in the developing complex systems, namely scale free networks, were also discussed. Hub like nodes (reusable components) that have large number of connections among a sea of nodes with fewer connections have biological equivalents in the brain. From the gene regulatory networks to the topology and interconnections within/between whole brain regions, it seems, scale free networks are at work.

Robust characteristics of scale free networks make them a prominent candidate for modeling approaches. For example, overall topology of a scale free network is not heavily affected from random deletion of nodes, making them suitable for both gene regulatory networks which require robustness against mutations as well as neural networks which require graceful degradation where random deletion of synapses does not have a prominent effect to the overall network behavior/topology.

In addition to this, small world networks were discussed. With the increase of brain size, wiring becomes much more costly. Brain has a *laminar structure* and hub like regions/neurons to reduce the wiring cost

while maintaining the small world property where any node can be linked to any other node in a small number of steps.

In the last section (5.5), a biological property of developing organisms was discussed. *Edge of chaos* is a way to create diversity while still tightly regulating a large subset of events from the level of cell cycles to the level of developmental time windows. Gene regulatory networks are dynamical systems and their phase space contains stable and unstable attractors. Kauffman's idea was that stable attractors can simply translate to the known cell types while unstable attractors can be used as the so called edge of chaos mechanism to create the required diversity, using only a small set of local interaction rules.

CHAPTER 6

6 An Evolutionary Developmental Model

In the previous chapters, several research directions were explored. In this chapter, a hybrid computer model which embodies some of the principles derived from these research directions will be introduced. The model can combine the advantages of evolutionary and developmental principles to explore the effects of local rules on cellular differentiation, retinal mosaics, layered structures and network topology.

There are various types of relevant modeling lines that seek biological plausibility and focus on one of the areas such as spiking neurons, self organization, gene regulatory networks and genetic direct/indirect encoding methods for evolutionary computation. After a literature survey on such models, the evolutionary developmental computer model designed and implemented by the author of this thesis will be introduced.

6.1 Computer Models with Varying Perspectives

A disparate set of perspectives and corresponding models exist. For example, NEURON focuses on the *realistic behavior* of a single neuron (Hines et al., 2007, Hines & Carnevale, 2000). NEURON simulates intricate anatomical and biophysical characteristics of a single cell, aiming to answer high level research questions of neuroscience. A similar

toolkit is Genesis, again aiming a realistic simulation of neuron behavior (Bower et al., 2007). Both NEURON and Genesis are capable of simulating networks of large sizes when running on a parallel computational architecture (i.e. a cluster) even though on a single computer they are aimed to simulate small networks. Topographica, on the other hand, focuses on *large scale structure and behavior* of networks or "topographic maps", introducing the idea of "neuronal sheets" as building units to create a more practical model (Bednar, 2009). Topographica can control the level of detail, because potentially being compatible with NEURON and Genesis, it provides an interface where neuronal sheets can be extended to more realistic models. NEURON made an enhancement to be able to efficiently simulate spiking neurons (Hines *et al.*, 2007). Spiking neural networks (SNN) focus on *time*, rather than biophysical properties. Consequently, spiking behavior of a neuron depends on the timing of incoming spikes which decay in time. To achieve a more complex behavior, stochastic components are usually added. Although none of the above models are intended for simulation of development and cellular differentiation, they allow high level and low level configurations which could be used in a developmental model (at least in theory).

There is a recent study which introduces a model where stochastic parameters in SNN are controlled with *genes*, affecting the overall spiking behavior of SNN (Soltic & Kasabov, 2010). The focus of Soltic and Kasabov's study is *computational neurogenetic modeling* where interaction between genes which control stochastic parameters in SNN, is simulated through time via gene regulatory networks. However, in this study, since genes only control the stochastic parameters, they have an "overall" effect on the spiking behavior of the whole network, rather than specific cell behavior. *Self organization* can also be a point of focus. For instance, using temporal rules which are analogous to the spatial rules of Kohonen's self organizing map (SOM), self organization of SNNs can be achieved. However, the self organization behavior in Soltic et al.'s study is basic and it only affects the connection weights.

Bottom up approaches such as *agent based* modeling are also worth mentioning, since they make use of local interactions. For example ABNNSim is suitable for research on self organizing topologies which can emerge from local rules. Even though neuron type diversity is ignored, it is demonstrated that extending the model for usage of spiking neuron instead of default neuron type perceptron is rather simple, making ABNNSim a candidate for more detailed models. It is also noteworthy that ABNNSim can use a medium for chemical signals such as adrenalin (Schoenharl, 2005).

More realistic developmental models also exist. For example, Zubler and his colleagues developed a simulation tool called CX3D, where physical interactions (depending on physical shape etc) between growing neurons and developing networks are taken into account (Zubler & Douglas, 2009). Another line of modeling exemplified by Zubler et al., is self organization and construction of state machine like *rule networks* which control cell behavior. This in turn allows their model to incorporate gene regulatory network like properties (Zubler *et al.*, 2011).

In the artificial life context, hybrid models that combine evolution and development exist. For instance, Nolfi and Parisi's work (1995) focuses on evolving neural networks that develop in time and represent an organism's nervous system. Their model translates genetic information into low level parameters that describe position of neurons, branching angle, synaptic weight etc. The developing network affects the organism's behavior. Organisms evolve in a virtual world where the fitness function is given by the number of collected “food elements”.

Kumar and Bentley's (2003) model, Evolutionary Developmental System (EDS), focuses on multi-cellular morphology. Using gene regulatory networks, their model generates cells that can organize themselves into certain shapes such as a line, a plane, a cube or a sphere. A similar but more recent model, GReaNs (Genetic Regulatory evolving artificial Networks) can use gene duplications to achieve higher complexity (Joachimczak & Wrobel, 2012). GReaNs explicitly focuses on

morphogenesis where self organization and differentiation of cells into various 3D patterns occurs. Although these models allow cellular differentiation and cell-cell interactions, they do not use neuron like cells or any connection scheme.

6.2 An Evolutionary Developmental Computer Model

As discussed above, highly diverse computer models exist in the literature. Therefore as the first step, three basic questions should be answered about the computer model developed in this study.

6.2.1 The ”What” Question

This model is *not* :

- a network of identical neurons or a neural network,
- a reverse engineering of visual system or retina,
- a simulation which mimics physical/chemical rules

This is:

- a hybrid evolutionary and developmental computer model written in C++
- a model of a developing network or rather a 'tissue' of progenitor cell types that later differentiate into other cell types such as neurons[20] according to neighborhood information
- a model that allows one to define and/or evolve local rules which are described in the DNA where these rules are indirectly translated into a network topology via cellular interactions.

6.2.2 The “Why” Question

This model incorporates ideas from both evolution and development. The design principles used in the model incorporates their combined

[20]There is relevant information in the genotype, describing cell types that may or may not connect to other cells i.e. glia vs. neurons, however the model mostly focuses on the connection scheme and ignores activation behavior.

strength. For example, in the developmental component, developmental parameters are configured by the DNA which allows an evolutionary model to use or change this information. If the modeler has no idea on the developmental parameters, (s)he can simply give the requirements in the form of a set of objectives (or fitness functions); then the developmental parameters will be searched by the evolutionary component of the model.

This model can be used as a pure developmental model as well as a pure evolutionary model. Moreover the evolutionary component can have either single or multiple objectives. In this thesis work, the model is used for the purpose of finding and/or configuring local rules that describe cellular level interactions (developmental component) as well as exploring high level properties such as lamination and wiring cost (evolutionary and developmental components). Building upon the previous configurations is, as illustrated in the results section, fairly easy.

This model contributes to the literature at least in two different ways. Firstly, it combines the advantages of *multi-objective optimization* and differential evolution (with modifications such as whole genome duplication, dynamic crossover rate etc.) with the advantages of developmental rules (regional identity, cellular differentiation, exclusion zones etc.). Since the design of the model is inspired from the evolutionary and developmental research on the visual system, the model has biological plausibility. Secondly, the model introduces a methodology to create/evolve cell types that can have highly specific behavior via addition of restrictive rules to the genome. This allows simultaneous existence of cell types that have different degrees of precision in their connection scheme[21]. Therefore, cell types are not predefined and in theory, infinitely many number of cell types can be generated. As a result, using this model, one can create a network which incorporates various cell types that have certain characteristics similar to known biological structures (such as retina).

[21]Different degree of precision is also possible in other cellular interaction rules, however they are not explored in this thesis work.

6.2.3 The “How” Question

As the third step, “how questions” are answered, and the methodology is described. Even though the model primarily focuses on local interactions between cells, the design of the model is inspired from the evolutionary, developmental and computational research on the visual system. Therefore, evolutionary and developmental components of the model use ideas such as division of labor, whole genome duplication, diversification and exaptation (chapter 2), cellular differentiation, exclusion zones and anatomical mosaics (chapter 3), a Gaussian connection scheme that depends on distance, reusability, control of entropy and precision[22] (chapter 4 and 5). While these ideas are incorporated in the model, some of the explored ideas (i.e. the edge of chaos idea) are not used[23].

For the evolutionary component of the model, differential evolution and multi-objective optimization methods were used. For the development component, a simple initial model was progressively improved via addition of biologically plausible developmental rules such as regional identity, new cell types with different connection aggressiveness, differentiation, source-target dependent connection scheme and finally cell popularity.

[22]Cell specification via evolution from a single generic cell type (i.e. heterogeneous addition of restrictive rules) bears resemblance to a multiresolution scheme.

[23]Not all discussed ideas are used in this model and an overall verbosity or an abundance of explored topics through the previous chapters was intentional for several reasons. Firstly, the author plans to extend the model. Therefore, some of the ideas such as edge of chaos will be incorporated in the model in the near future. Secondly, an overall exploration of the multi-disciplinary literature by itself can be useful for other researchers. Finally, throughout the thesis, there were certain testable predictions conjectured by the author (i.e. proliferation still depends on aerobic glycosis because of the reusability idea, that is, proliferation still depends on the regulatory role of some of the components that belonged to an ancient genetic toolbox that controlled aerobic glycosis, (see chapter 3 discussion section), or *joint entropy idea as an evolutionary constraint for the emergence of a multiresolution like scheme* in the visual system and possibly in higher levels of cortical organization (i.e. where and what pathways), see subsection 5.3.1). Although certain amount of verbosity was inevitable, this ideas may stimulate other research that is not necessarily relevant to modeling yet relevant to deep evolutionary, developmental and computational principles that affect and constrain not only the visual system but also cognition and the brain.

Evolutionary Algorithms

Evolutionary computation finds solutions in a large search space by simulating evolutionary aspects such as reproduction, competition and natural selection. It is a way of freeing the modeler from the burden of dubious assumptions (especially if little is known about the optimal solution). Evolutionary computation is also useful when the modeler has more than one purpose and aims to explore the search space. For this reason multi-objective optimization methods can be combined with evolutionary algorithms. The computer model implemented for this thesis work uses differential evolution and multi-objective optimization.

Differential Evolution

Differential evolution (DE) is a simple and popular evolutionary algorithm that uses difference between two individuals to evolve another individual. The genotype information is usually encoded as floating points. DE is self adaptive since, after a number of iterations, the differences between individuals will diminish and the population will converge.

In the implementation, DE starts with a random population and randomly selects three vectors, denoting the genotype of three individuals, I_1,I_2 ,I_3. For each dimension *i* , I_4[i] is given by

$$I_4[i] = I_1 + M(I_2[i] - I_3[i]) \quad if\ \rho < CR \qquad \text{(Equation 6.1)}$$

$$I_4[i] = I_1[i] \quad if\ \rho \geq CR \qquad \text{(Equation 6.2)}$$

where M is the mutation scaling factor and CR is for controlling crossover rate. If the random variable p is smaller than the crossover parameter CR, then I_4[i] depends on the difference between the second and the third individuals as well as the scaling factor.

Modifications to DE

In the traditional version of differential evolution (*DE/rand/1/bin*[24]) CR and M are fixed (Kukkonen, 2012). However, in this model CR is updated

[24]DE/rand/1/bin is the name of the default differential evolution algorithm used by DE community.

according to the *acceptance rate.* Acceptance rate describes whether recent individuals which were created via above method were fit enough.

Acceptance rate is a dynamical variable that changes after each decision. If the individual is accepted, it “jumps”, if the successively more individuals are rejected it decreases gradually, approaching to a minimal value. CR changes according to the acceptance rate, if the rate is low it increases, if the acceptance rate is high, it decreases (*similar to a homeostatic mechanism*).

Another change in the traditional DE in this model is local search. When CR value becomes low, the probability of local search slightly increases. Therefore, if a new individual is accepted, acceptance rate jumps and CR rate decreases instantly. This allows a higher chance for local search around the newly found individual. However, after a short period of time, if no new individual is accepted, CR value and acceptance rate returns to the normal. Therefore Equation 6.2 was updated into

$$I_4[i] = I_1[i] \pm \sigma \qquad if\ \rho_{local} \leq CR/K \qquad \text{(Equation 6.3)}$$

Where σ is a small random value for local search around a randomly chosen individual I_1 and K is a constant. Acceptance of an individual is generalized into more than one fitness function using multi-objective optimization as described in the next subsection.

Multi-objective Optimization

In the computer model, a simple version of multi-objective optimization method was used for the purpose of finding a set of solutions that is close to pareto-optimal or close to the pareto front. A pareto-optimal set of solutions contains all solutions that represent “best possible compromises” between different objectives (Kukkonen, 2012).

The implementation used several rough versions of heuristics such as weighted summation of each parameter, elitism, finding knees and greedy approaches as well as diversity maintenance mechanisms that are configurable via weights. Therefore, the multi-objective method itself

had a genotype. To find the best mix of approaches, “individuals” *which themselves are “multi-objective optimization methods” with different focuses on diversity maintenance, elitism etc.* were evolved (using a simple test problem to check whether they converge at a local minima or find global minimum) and the genome of individual with the best performance were used for other problems.

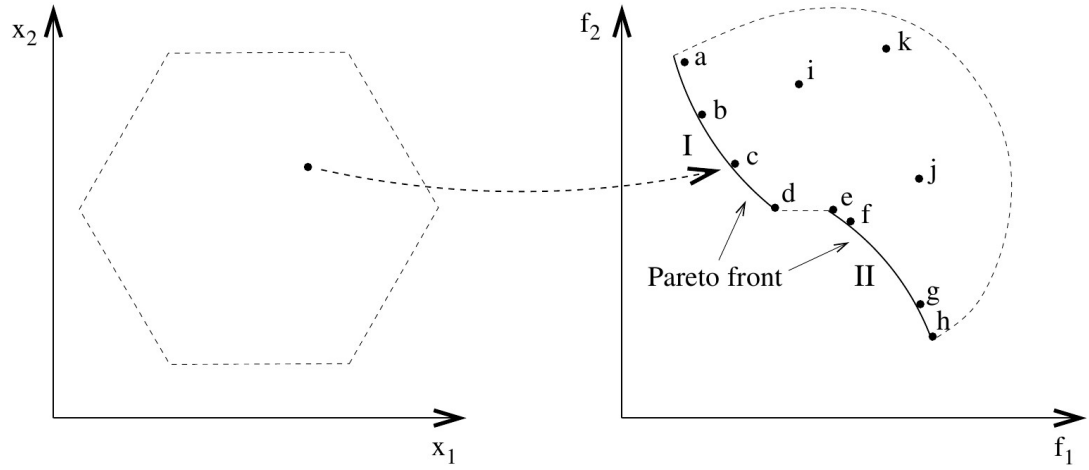

Figure 6.1. Pareto front in a biobjective problem

Solution candidates for pareto front are given in the bounded area

(Kukkonen, 2012, p.23)

No Free Lunch theorem (NFL) forbids a method to be optimal for all types of problems. However, in the scope of this thesis, finding the global minimum in a reasonable amount of time was the only requirement. To guarantee convergence, two key conditions were taken into account:

- Elitism (always keeping the best candidates for pareto-optimal set)
- Potential to fully explore the search space

Elitism check is done before the decision of whether to discard an individual. To ensure the exploration, another random variable is used in a similar manner to Equation 6.3. It is used with a small probability in the nonlocal search. Unlike the σ in Equation 6.3, this variable had a much larger variance to ensure full exploration of the search space.

Indirect Genetic Encoding of Cellular Interactions

Unlike a direct genetic encoding method where the network topology is directly encoded into the DNA, indirect encoding does not store the topology information in the DNA. Instead a "*recipe"* that consists of developmental rules which describe how to *build* the network is stored. In this computer model, the recipe consists of restrictive local rules that describe cellular interactions and connection schemes.

Any system that displays regularity and/or predictability has an underlying set of restrictive rules that describes the interactions between its components. Restrictive rules reduce the possible ways of interactions. Thus, restrictive rules or s*pecializations* are mechanisms to reduce *entropy*. Specialization can be described as a process where initially large imprecisions at certain aspects progressively diminish. For example, developing organisms require an elaborate balance between complexity and regularity. To achieve that, development starts with stem cells which have high "expressive power". However, at later steps, higher organization requires *specialization* of cells. Consequently, cells differentiate into more restrictive forms.

Behaviors of the differentiated cells are more predictable and therefore they are easier to control. Brain development also follows a similar trajectory where number of initial connections later diminishes to half and the overall circuitry acquires a higher amount of *precision*. Since achieving precision requires cells to specialize, evolution of various cell types with different characteristics and various levels of specialization is possible[25].

Overall, to achieve precision, direct rules are not always needed, especially if there is a developmental component. In this model, an indirect encoding method which mostly consists of local restrictive rules,

[25]The idea of using restrictive rules to *control* the amount of precision (i.e. cell types with varying specialization levels) was inspired from the information theoretic principles (i.e. entropy and multiresolution scheme) discussed in sections 5.1 to 5.3. as well as the division of labor idea discussed in 2.1.3.

is used for the differentiation of cell types and the development of the later network circuitry.

Simplest Local Rules and The Initial Model

For test purposes, an initial model that used a connection function with a Gaussian connection scheme[26] to decide the range and interval of connections between source and target cells was implemented. While this initial computer model could make use of the distance information and it was possible to use different connection functions, there were no cell specific interactions. Therefore, all cell types behaved the same. This will be referred as *default behavior* in the next subsections.

Later, more elaborate versions that used indirect genetic encoding methods to represent other cellular level interactions was build upon the initial model. These models were tested using a developmental scenario where progenitor cells with initial types later could differentiate into more specific types according to local interactions between cells in close neighborhood. To have an idea on the topology of the network, overall distribution of the connections were tested in all versions. Moreover the resulting network was rendered using a visualization library (see Visualization subsection below).

Whole Genome Duplication

Through the evolutionary history, researchers believe that there were several *whole genome duplications*. The advantage of a whole genome duplication is the preservation of the underlying gene regulatory circuitry for vital processes, while experimenting on the redundant (duplicate) parts (Hoyle, 2011). In 2.3.1, duplication was recognized as a means to achieve higher complexity.

This computer model allowed (and used) whole genome duplications. To achieve that, a finish “codon” with a special value was added to the end of genome. The length of the genome was small in the initial random

[26]The probability to make a connection decreases with distance.

population. In the reproduction phase, when the finish codon of I_1 was reached (see Differential Evolution subsection above), with a small probability, whole genome duplication occurred. This could happen until the genome length was increased into a predefined limit. To control the increase of size, a fitness function could forbid/punish long genotypes (see Results section below). Another motivation for whole genome duplication in this model was to *reuse* the earlier genotype and add new behavior *upon* the old ones. (See section 5.4 for more details on the reusability principle).

Layered Initialization

In sections 3.1.5 and 3.2.1, development of cortical layers and retinal layers were discussed. (It seems, *waves* of migrating cells form these layers). Moreover, in 3.1.2 the idea of regional identity[27] was discussed. Cells migrating to each layer had regional identities. Therefore, in the implementation of the model, it was assumed that initially each layer had a subset of progenitor cell types. Progenitor cells could later differentiate and take their final form. The model *skipped* the cell migration phase; that is, half way specialized progenitor cells were directly generated in different layers. The information regarding the number of layers was acquired from the DNA[28].

Differentiation and Radius of Interaction

In the model, the “radius of interaction” for each cell type was translated from DNA. The amount of acquired neighborhood information was cell type specific. The acquired neighborhood information was used for the progenitor cells to differentiate into more specific cells types.

[27]Even progenitor cells partly achieve regional identity. They can become half way specialized.

[28]In a more realistic model, these processes (migration and formation of layers) can be controlled via gene regulatory networks. This computer model did not use gene regulatory networks. Therefore, the exploration of one of the principles discussed in chapter 5, Kauffman's edge of chaos idea, were left as a future work (see section 5.5).

Stable attractors in the phase space of gene regulatory networks correspond to stable cell types (see section 5.5). The model allowed certain cell types to differentiate into stable types by using exclusion zones[29]. Differentiation depended dynamically on the neighboring cells.

Source-target Restriction

Source-target specific restrictive information was also kept in the DNA[30]. Since this model was built upon the initial simplistic model where connections were determined according to distance, source-target rules brought some constraints on the distance rule. Initially, source-target information was more generic. Any type of cells were able to connect any type of cells. Addition of new source-target rules therefore had *inhibitory* effects, preventing connections between specific cell types. Consequently, source-target rules served as restrictive rules to create more specific cell behaviors. Initially, whole genome duplication had practically *no* effect on source-target information. Yet, after mutations, a source cell type could acquire new restrictions on target types instead of a more general connection behavior.

Aggressiveness

Instead of a more direct implementation of a connection function, all cell types connected to their distal and/or proximal targets with a type specific probability which depended on DNA and distance value. As explored in subsection 4.3.1, it is plausible that cells (such as retinal ganglion cells and simple cells) use a connection scheme that depends on distance. However it is also known that there are other *restrictions*, that can potentially lead to structures such as receptive field mosaics (see subsection 3.2.3). This requires *construction rules* (i.e. source-target restriction, exclusion zones) which intrinsically enable the creation of anatomical mosaics.

[29]More detail can be found in Retinal Mosaics subsection under 6.2.4.

[30]Source and target *do not* correspond to indexes or positions of cells. They correspond to specific types of cells.

Greed

Cell type dependent tendency to make new connections with other cells is called greed. If a cell type has high greed value, it will have more chance to make new connections. Cell types with high greed value generally had more axonal (and optionally dendritic[31]) connections.

Cell Popularity

As discussed in 5.4.1, having hub like nodes[32] in a network, generally results in robust properties and brain circuits and gene regulatory networks display such properties. Therefore the model incorporated a means of control for creating networks with hub like nodes. A simple approach to create hub like nodes was to assign a fitness or popularity value to the target cell before deciding whether to connect *or not*. In developmental terms, the fitness value may depend on the amount of secreted and received neurotrophic factors (see subsections 3.1.8 and 3.1.9).

DNA

DNA consisted of floating point values. Encoding of restrictive rules with various scopes was possible. *Default rules* were encoded at the beginning of the DNA as below:

> {#layers, differentiation time window, short range aggr, long range aggr, dummy, ... , dummy[33]}

First floating point element was translated into number of layers at the beginning of the development [34]. Second element controlled the duration

[31]The model allowed configuration of greed value explicitly for axons, dendrites or both.

[32]Hub like nodes are common to both scale free and small world networks.

[33]The model supports extension of new default rules, because the DNA is processed as blocks of 4 elements. After addition of new default rules, if the length of overall default rules is not divisible by four, dummy rules are added.

[34]There will be certain changes in the encoding when gene regulatory networks are introduced in the near future.

of the differentiation process. Third element controlled the tendency to make close by connections (i.e. *how close is too close*). Fourth element controlled the tendency to make long range connections (i.e. *how far is too far*). Type specific radius of interaction for cellular differentiation was also stored in the DNA:

{r_1, r_2, ..., r_k, dummy,...,dummy[35]}

For k different cell types, k different interaction radiuses were defined.

Whole genome duplication allowed exaptation into new source–target rules. Source-target rules were represented as blocks of four elements:

{source type, target type, short range aggr, long range aggr}

Source-target rules had restrictive roles on the overall connection scheme (reducing overall entropy, see subsection 6.2.4).

After whole genome duplication (and mutations), new source-target type specific restrictive rules were created. That is, duplicate default rules and radius of interaction rules later became source-target rules via exaptation. Secondary and later duplications initially had no effects, yet, after mutations new restrictive rules were emerged and more specialized cell types evolved. Below is a sample DNA:

{1.95559 0.942985 1.46869 1.98658 1.37547 1.78545 0.322011 1.83782 1.60741 1.17164 1.29342 0.372859 1.37088 1.86503 1.559 1.90499 1.40935 0.589819 0.886342 1.54457 1.77957 0.847671 1.41514 0 0.253119 1.0497 0.903606 1.14618 0.104051 0.718838 0.497239 0.424195 -100[36] dummy,..,dummy}

A Quick Summary of Events

In the evolutionary component of the model, the population started with individuals that had randomly generated DNA (with minimum length and no restrictive rules). Then, for each individual, the genetic information was translated into phenotype via developmental rules described above (i.e. networks with different default aggressivenes value, different

[35] For best performance, number of cell types and therefore number of radius of interaction elements were kept as multiples of four.
[36] -100 denotes the end of genetic information

number of layers, different radius of interaction rules). In the next step, a fitness value was assigned (i.e. wiring cost) to each individual. Individuals with better fitness values were accepted into the next generation using the methodology described in Multi-objective Optimization subsection. Then, new individuals were generated using the methodology described in Differential Evolution subsection. With a small probability, whole genome duplication occurred, DNA size doubled and (via either exaptation or mutation) new source-target restriction rules were generated. After several generations, the population converged into a set of genotypes that had acceptable fitness values.

Visualization

For the visualization of resulting network topologies and cell types, Open Scene Graph (OSG) was used. OSG is a high performance graphics library written in C++ and OpenGL. It allowed visualization of large networks.

6.2.4 Results

Several tests and scenarios were applied to the initial and successive models. They will be discussed in a chronological way. Initial versions of the model only used the developmental component. The evolutionary component was used only in the last two scenarios.

Initial Model

The initial model defined the default behavior of any cell. There were no restrictive rules and the default behavior was to greedily connect any nearby cell with a connection probability that decreased with distance[37]. In Figure 6.2 below, initial model is compared to a random connection scheme where connections were completely random (therefore they did not depend on distance).

[37]This idea was inspired from the research on the computational/conceptual properties of the visual system. See subsection 4.3.1 and Simple Cells for more details.

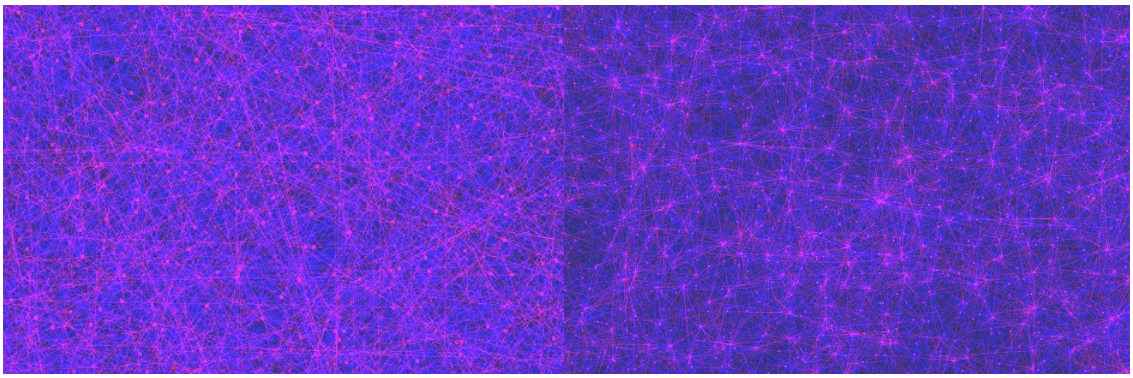

Figure 6.2. Random vs default connection scheme

(Left) Connection scheme is completely random. (Right) One can observe an overall lack of long range connections, cells tend to connect other close by cells, forming local clumps or clusters of cells that are highly connected and blank regions where cells are too far to connect each other.

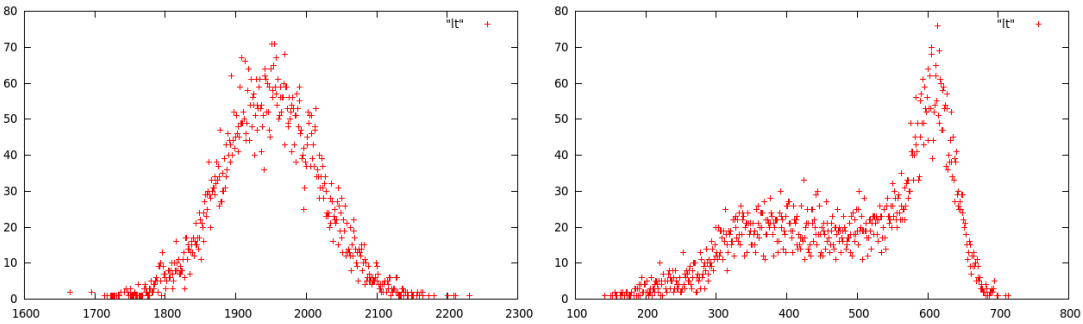

Figure 6.3 Random vs default connection scheme[38]

(x: # connections, y: # cells)

Default connection scheme reduced the number of connections between distant cells. Since cells that were closer to each other would make more connections, overall connection distribution was not a Gaussian anymore.

[38]Using hard coded configuration parameters (within the implementation), *shifting and scaling* of the connection distributions were possible. Therefore, even initial model could generate different connection distributions and the illustration given above was only one of the possibilities. For the sake of consistency, the configuration parameters that generated the distribution illustrated above were kept constant in the later scenarios below.

When default connection distribution was plotted for axons and dendrites separately (Figure 6.4), scatter plots demonstrated that neither outgoing connection (axonal) *distribution,* nor incoming connection (dendritic) distribution was Gaussian[39] [40]. Therefore, in accordance with the distance function used in the default connection scheme, some cells *sent* and *received* substantially more connections than the others[41].

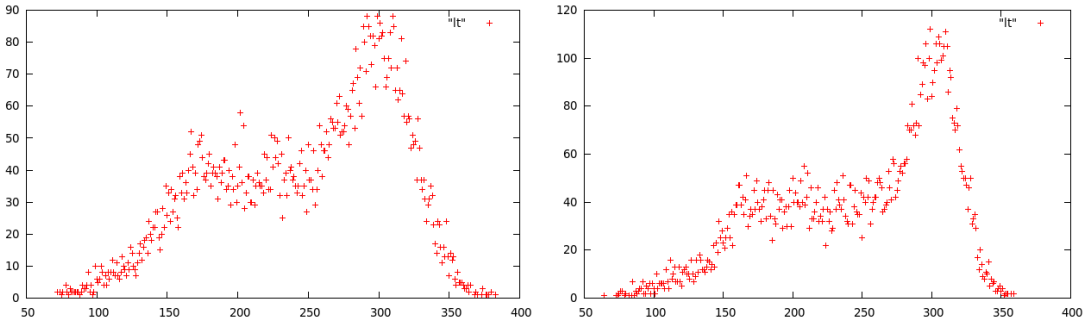

Figure 6.4. Default connection scheme

(Left) axonal distribution (x: # outgoing connections, y: # cells)
(Right) dendritic distribution (x: # incoming connections, y: # cells)

Introduction of New Cell Types

Initial model had only a single cell type. Greed value therefore had no visible effect. Addition of new cell types that had type-specific greed values resulted in a visible effect in the distribution depicted in Figure 6.5.

[39]This can be interpreted as a decrease in overall entropy, since the connection scheme was less random, number of possible configurations was decreased.

[40]While the initial model did not display a difference between axonal and dendritic distributions, in the later versions of the model, different axonal and dendritic distributions were observed according to the local rules that were introduced. Therefore the model is capable of creating cell types that have unbalanced axon/dendrite ratio.

[41]This demonstrates that a connection scheme that depends on distance can create a connectivity bias *depending* on the 3D network shape, since neurons that are positioned at the center of the network would have more chance to make connections, unlike the neurons at the boundaries.

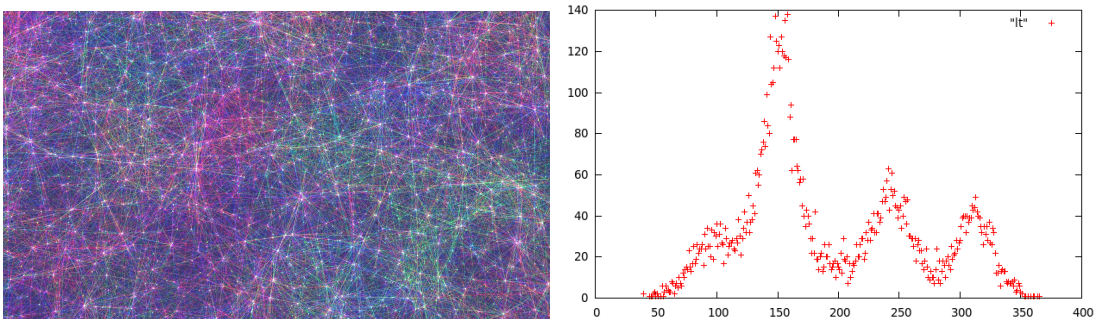

Figure 6.5. Default connection scheme + 2 new cell types

(Left) Visualization of the resulting network, with different colors for different cell types. (Right) Overall connection distribution. Addition of 2 new higher greed values is also fairly visible in the distribution (compare to the initial model).

Addition of Type Specific Connection Scheme

Type-specific connection scheme required restrictive source-target rules that were defined in the DNA. Consequently, using randomly generated DNA (in several trials), observation of various connection distributions was possible[42].

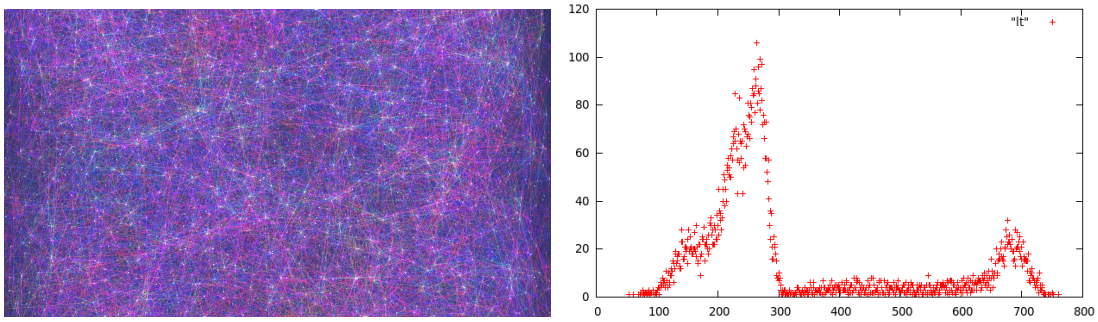

Figure 6.6. Type-specific connection scheme

(Left) Restriction of connections between specific source-target cell types is possible. Compared to Figure 6.5, this visual lacked almost all of the *green* connections. (Right) Connection distribution that displayed a restriction on connections, nullifying the effect of type specific greed value of at least one of the cell types. (x: # connections, y: # cells)

[42]The usage of evolutionary component was not necessary.

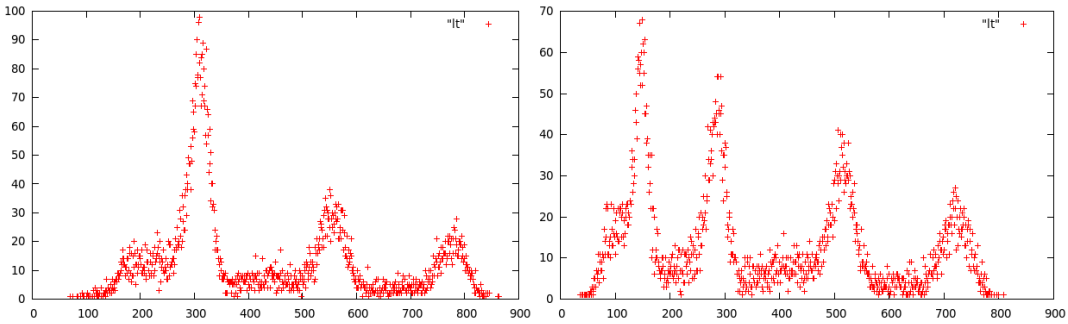

Figure 6.7. Other type-specific connection scheme possibilities

Different source-target restriction rules and cell types resulted in different connection distributions. (x: # connections, y: # cells)

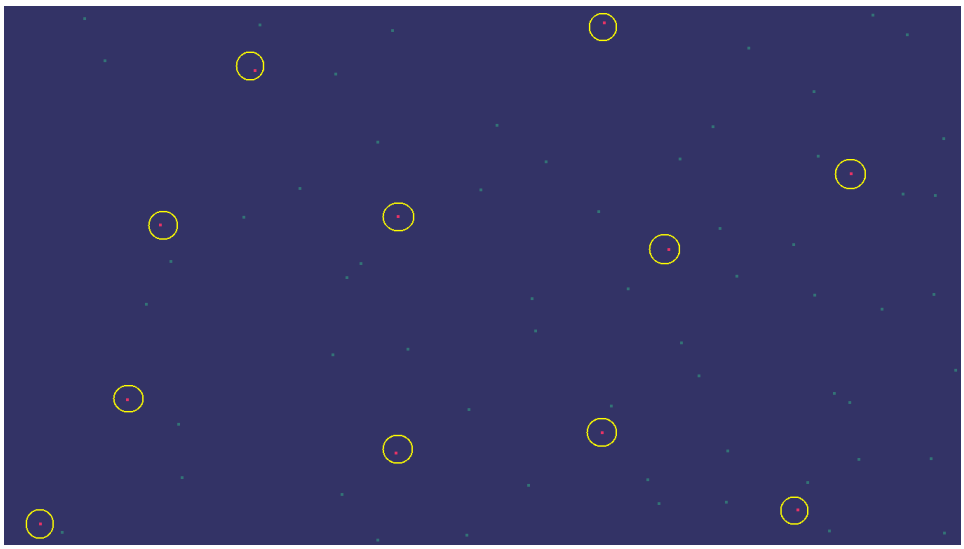

Figure 6.8. Retinal mosaics

S cells are circled. (Circles do not represent the exclusion zone) The radius of the exclusion zone is *approximately* the distance between two closest S cells.

Modeling Retinal Mosaics

Self organization ideas on differentiation were tested using a simple scenario in which progenitor cells of a single type differentiated into either a primary (P: green) or secondary type (S: red) cell. The self

organization rule was exclusion zones[43] that had certain radius depended on the DNA[44]. Differentiation into P cells occurred if there were no other P cells in the exclusion zone. If there was a close by P cell, then differentiation into S cells occurred. This can be considered as a simple simulation for the emergence of retinal mosaics[45] (see Figure 6.8).

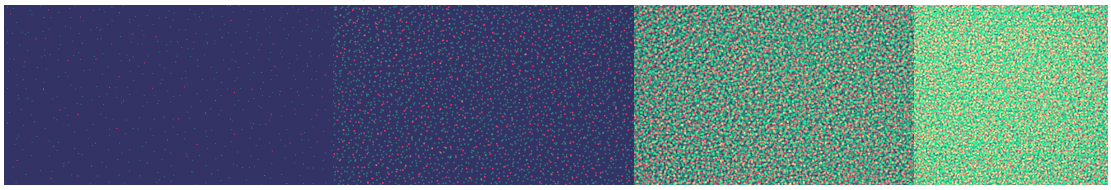

Figure 6.9. Retinal mosaics (zoomed out)

The overall ratio of S cells is small, therefore zooming out (left to right) reveals a dominant green color (the color of P cells). Total number of cells was around forty thousand.

For comparison, Figure 6.10 below depicts another individual where radius of exclusion adjusted to a small value to prevent the mosaic effect.

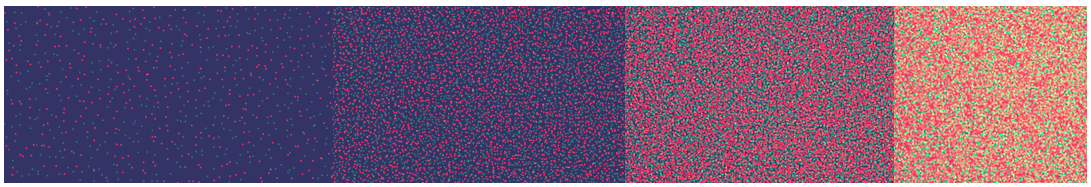

Figure 6.10. Retinal mosaics (zoomed out)

The overall ratio of S cells was large, since the radius of exclusion zone became too small. Rather than in a mosaic form, cells were randomly differentiated. Therefore zooming out (left to right) reveals a yellowish red color (which is the mix of green (P) and red (S) colors).

[43]In this scenario, "radius of interaction" value stored in the DNA defined the radius of exclusion zones.

[44]Although individuals were always initialized via DNA, in this scenario and the previous cases, multi-objective optimization and differential evolution were not necessary. Therefore, DNA consisted of user defined values. The model also had some stochasticity.

[45] For more information on mosaic organization via anatomical rules, see 3.2.3.

Emergence of A Mosaic Network

Combining above version of the model with the initial default model resulted in emergence of cell types that differentiated according to exclusion zones and created a mosaic connection scheme, as illustrated in Figure 6.11. As previously discussed in subsection 3.2.3, receptive field mosaic formation may be primarily determined by the formation of *anatomical mosaics* (Anishchenko *et al.*, 2010). A proposed theory was that anatomical mosaic formation could be achieved via type-specific neighboring cell interactions (Fuerst et al., 2008).

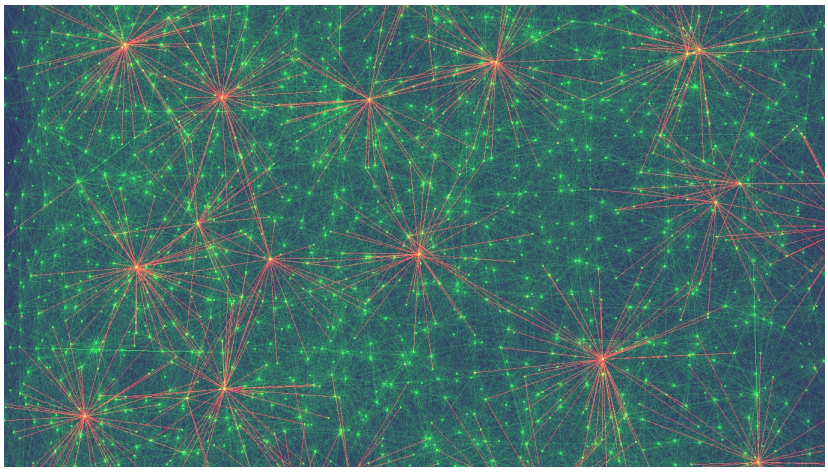

Figure 6.11. Retinal mosaics like differentiation

Red cells illustrate differentiated cells. Similar to S cells described in the previous subsection, red cells differentiated according to exclusion zones.

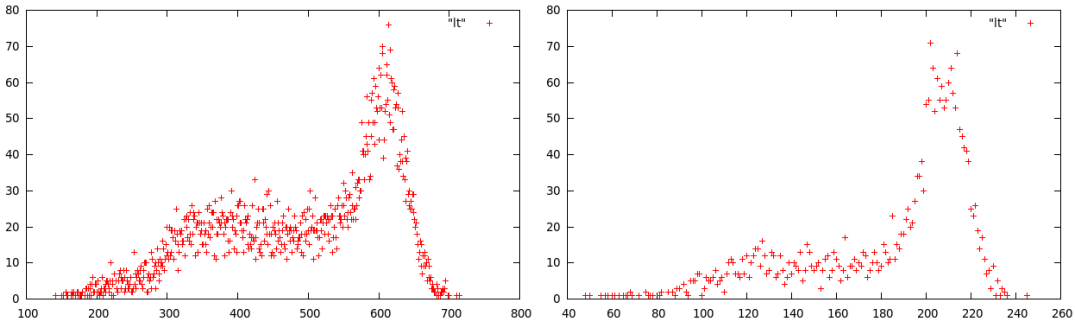

Figure 6.12. Comparison to default connection distribution

(Left) Initial model, (Right) Mosaic network. As one may observe, connection distribution did not change. The only change to the initial model was the addition of the differentiation rule. (x: # connections, y: # cells)

Addition of type specific greed and aggressiveness value resulted in highly aggressive and greedy, hub-like neurons.

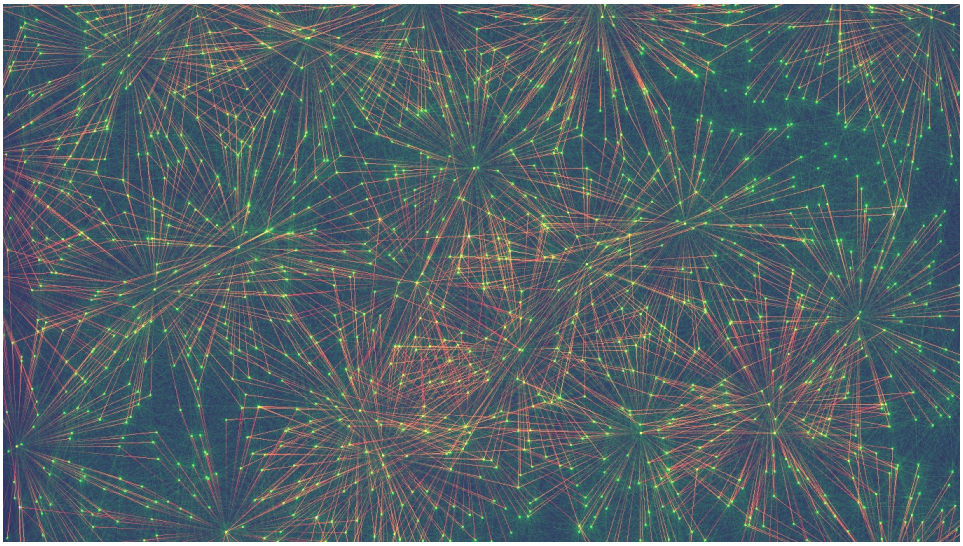

Figure 6.13. Emergence of hub-like neurons

Compared to Figure 6.12, red cells became more aggressive, they made more long range connections and overall number of connections made by them were also increased. Green cells remained the same.

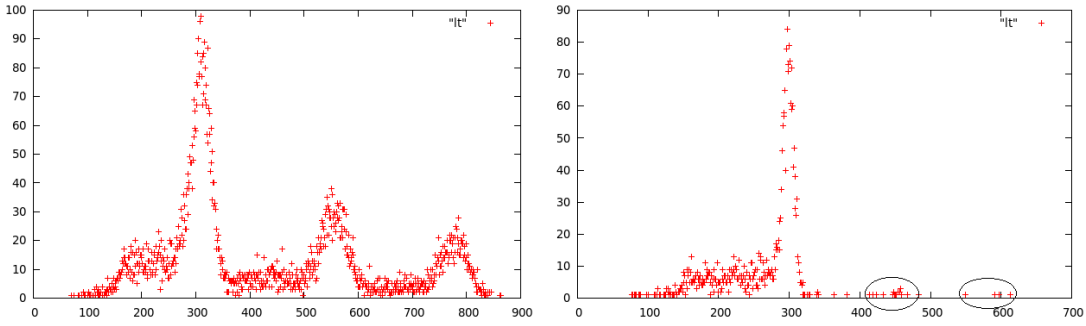

Figure 6.14. Comparison to type specific greed and aggressiveness

Compared to the previous version of the model that did not use differentiation (see figures 6.5, 6.6 and 6.7), greedy cell types were mostly differentiated into default types (P cells that were colored green). Only a handful of them (circled in the right) were able to maintain, due to the exclusion zones. Those cells gained hub-like properties since they had relatively high greed and aggressiveness values.

Cell Popularity and Resemblance to Scale-free Networks

Assigning fitness or popularity value to cells according to some criteria, and deciding whether to connect or not according to this value resulted in an even more segregated network of cells that made several connections and cells that remained mostly isolated.

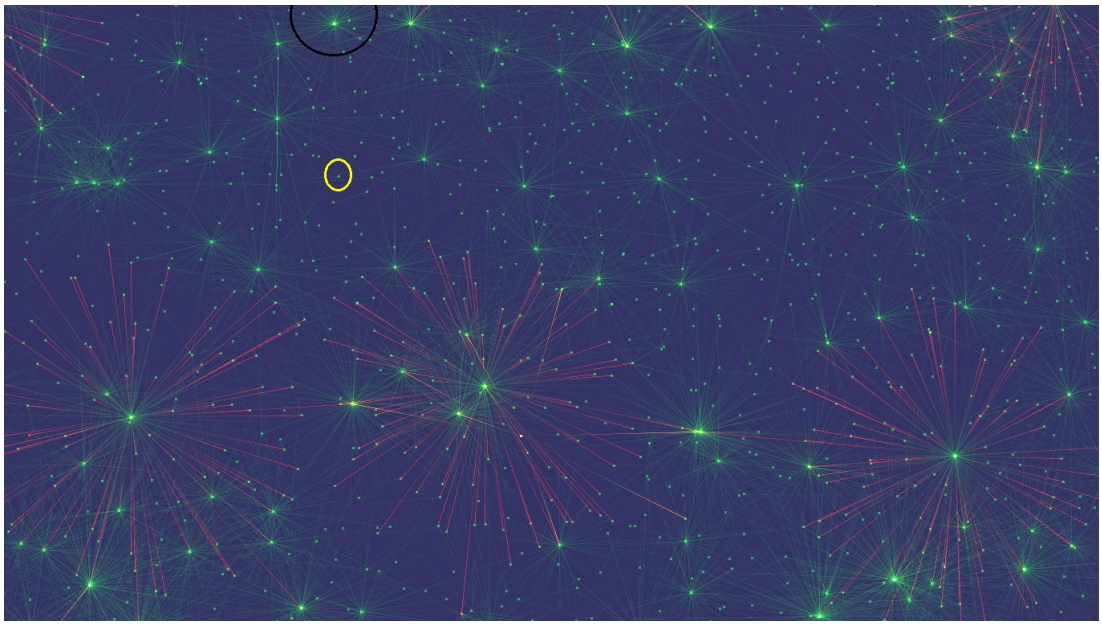

Figure 6.15. A network of admirers

Notice that some of the green cells on the background had almost no connections (circled in yellow). Moreover, aside from red cells that made red connections, green hub-like cells also emerged (circled in black).

Admiration

Admiration rule was conjectured as following: A source cell had an increased tendency to make connection as the assigned fitness value to the target cell increased[46] (see Figure 6.15). For testing this idea, a fitness value[47] assigned to the target cell as below.

$$f_{target} = s_{ag} n_{sd} + t_{dg} n_{td} - c\, n_{sa} \qquad \text{(Equation 6.4)}$$

Fitness value depended on axonal greed of source cell (s_{ag}), dendritic greed of target cell (t_{dg}) number of dendrites source cell had (n_{sd}) number of dendrites target cell had (n_{td}) number of axons source cell had (n_{sa}) and a constant value c.

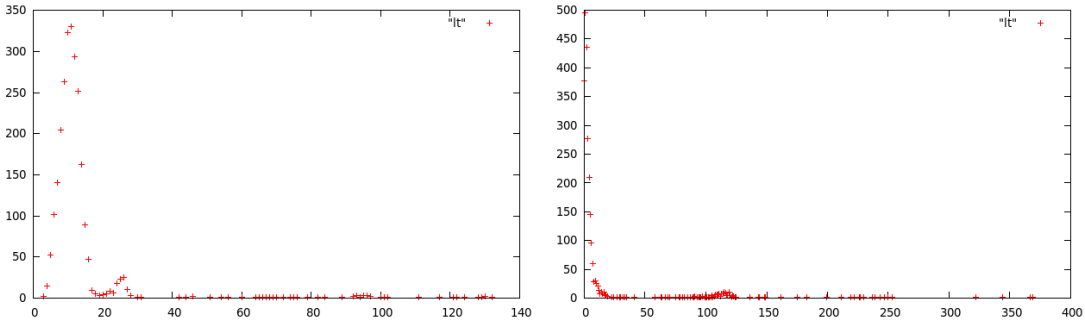

Figure 6.16. Axonal and dendritic connection distributions

Axonal (left) and dendritic (right) connection distributions demonstrated a highly segregated connection scheme. (x: # connections, y: # cells)

Since the network contained hub-like cells as well as a high number of poorly connected cells, overall connection distribution *resembled* a power law distribution. (At least, when compared to Figure 6.14, the distribution was much closer to a pareto distribution; notice the long tail).

[46] This idea was inspired from the research on scale-free networks, see subsection 5.4.1 for more information.

[47] There can be several ways to assign a fitness value. Equation 6.1 used only source-target specific information. However a fitness function that uses target information and information retrieved from a randomly selected cell instead of source may also be plausible.

Jealousy

Jealous rule was the opposite of the admiration rule and conjectured as following: A source cell had an increased tendency to make connection as the assigned fitness value to the target cell decreased. The fitness function was conjectured as below[48].

$$f_{target} = c[n_{sa} + n_{ta}] - s_{ag} n_{sd} - t_{dg} n_{td} \qquad \text{(Equation 6.5)}$$

Fitness value depended on axonal greed of source cell (s_{ag}), dendritic greed of target cell (t_{dg}) number of dendrites source cell had (n_{sd}) number of dendrites target cell had (n_{td}) number of axons source cell had (n_{sa}), number of axons target cell had (n_{ta}) and a constant value c.

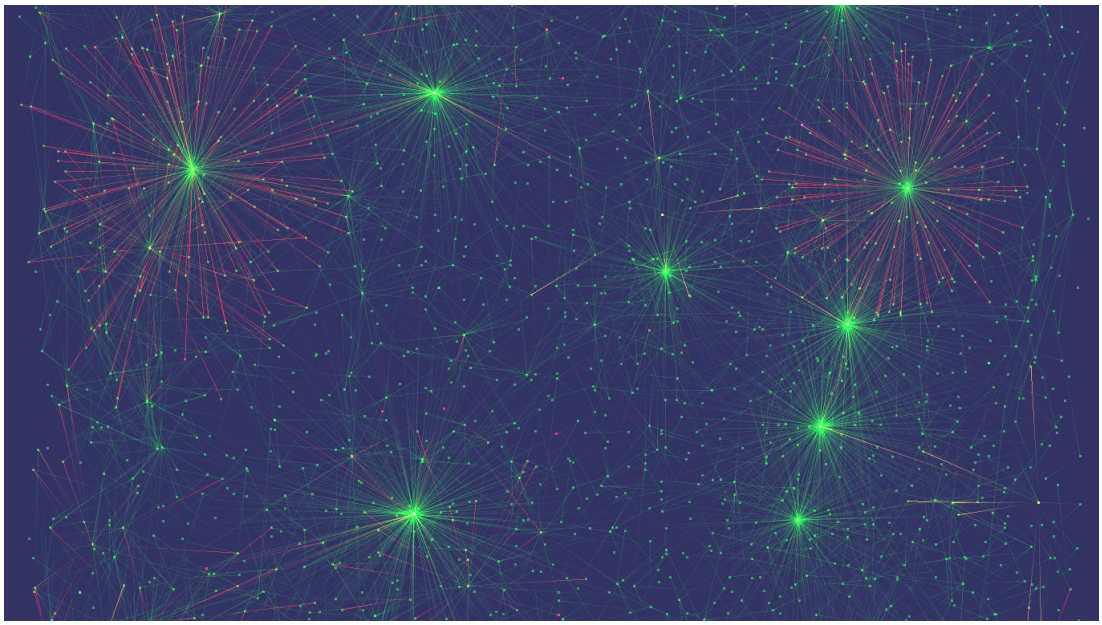

Figure 6.17. Scale-free network effect amplified

This new rule, resulted in a network that contained few cells that dominated the network as well as few cells with mediocre amount of connections. The remaining cells all had very small amount of connections if not none.

[48]Changing the sign of the fitness function would result in admiration rule, therefore they can be generalized into a single cell popularity rule. However, the author plans to extend the model to simultaneously incorporate cell types which have admiration and cell types which have jealousy behavior. Therefore, they were introduced as separate rules within the cell popularity context.

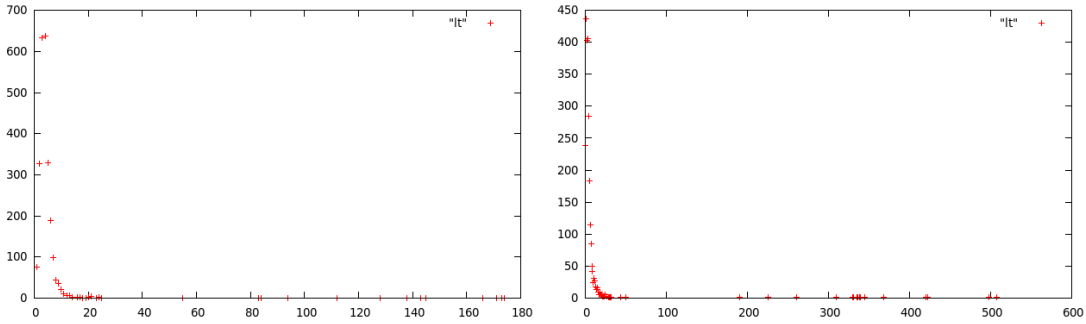

Figure 6.18. Axonal and dendritic connection distributions

Axonal (left) and dendritic (right) connection distributions demonstrated even more segregated connection scheme. The tail is longer in both distributions when compared to Figure 6.17. (x: # connections, y: # cells)

Overall, popularity rule were used for creation of non-homogeneous network properties. The easiest to observe effect was emergence of scale-free network like properties (i.e. a distribution with a long tail and hub like cells). However, the model allowed many other connection schemes by changing the proposed fitness functions. For example, another fitness function for jealousy rule could generate effects such as cell types that had unbalanced axon/dendrite ratio.

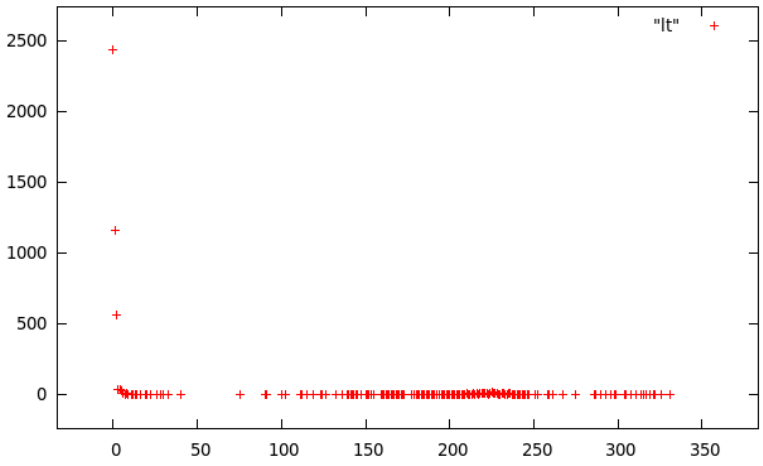

Figure 6.19. Scale-free like axon distribution (low entropy)

The scatter plot resembled a power law distribution

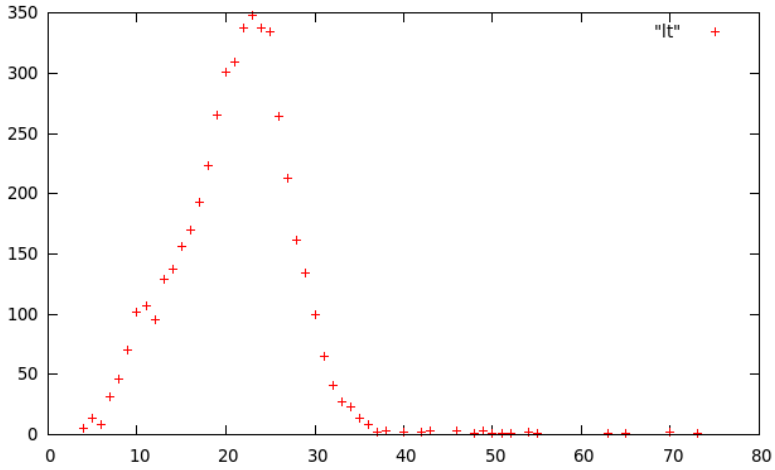

Figure 6.20. Dendrite distribution of the same network (high entropy)

Compared to axonal connection scheme in Figure 6.19, dendritic connection scheme was less precise (high entropy) and therefore more similar to a Gaussian.

The fitness function that generated such a connection scheme was simple (yet effective).

$$f_{target} = c\, n_{ta} - s_{ag}\, n_{sa} \qquad \text{(Equation 6.6)}$$

Fitness value depended on axonal greed of source cell (s_{ag}), number of axons source cell had (n_{sa}), number of axons target cell had (n_{ta}) and a constant value c. If the target high number of axons, connection probability decreased, therefore the overall number of feedback connections decreased compared to the previous scale free like network[49].

Because number of axonal connections vs number of cells resembled a power law distribution (i.e. Figure 6.19 resembled a pareto distribution) and dendritic connection distribution were mostly random, this created an axonal connection bias within the network. That is, this connection

[49]Unlike the previous hub like cells that had high number of both axons and dendrites, in this network, the probability to connect to a cell was not proportional to the number of axons the target cell had (see Figure 6.20). Therefore the number of feedback connections was reduced while the network still maintained a hierarchical structure due to the power law like distribution of axonal connections.

scheme allowed evenly spreading information to the whole network in a roughly feed forward manner (because of the decreasing number of axons and lower probability for feedback connections) starting from a relatively few number of cells (that had high number of axonal connections[50]).

Layered structures

Sample images illustrating layered structures are given below:

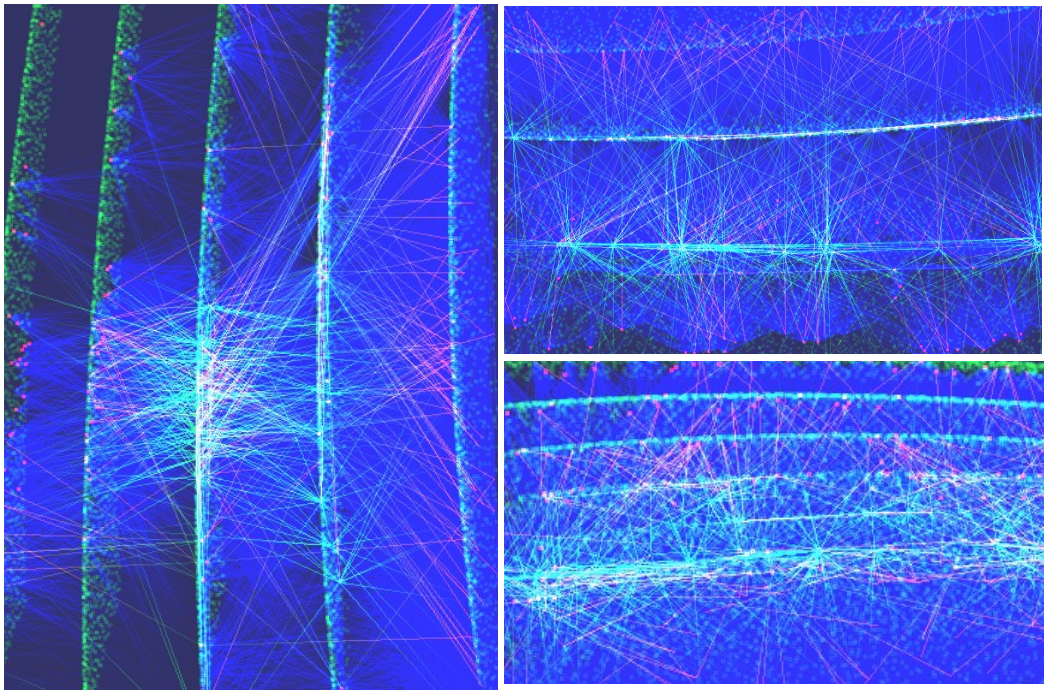

Figure 6.21. Layered organization

Number of layers were controlled by DNA and progenitor cells were directly positioned in layers (without migration) with slightly randomized positions. Layered structures were 3D and the distance between cells in different layers was accordingly calculated. Different sets of progenitor cell types were used in each layer. However, the resulting configuration still mostly depended on the differentiation phase and the DNA. (Like retina, exclusion zones were used to determine cell fate). As one can see from the figure, there exist different cell types with different connection

[50]Because these cells have high number of axons, they can be used for a top down spread of information within this emergent hierarchical network structure.

schemes. Edges in the figure that have halfway changing colors depict connection between different cell types.

A Simple Evolutionary Test

Wiring cost is known to be a critical constraint in the mammalian brain. Even though the simulated network generally consisted of a rather small number of nodes, keeping the wiring length minimum may have certain advantages.

The differential evolution component of the model was tested using a *single* fitness function that returned a better fitness value (*closer to 0*) if the network had a smaller wiring length ratio. It turned out, such a scenario favored *short range connections* instead of longer range connections and also *lamination* and a larger DNA with more *restrictive rules*. Number of layers were specified by DNA, therefore networks with different number of layers evolved.

Table 6.1. Wiring cost vs lamination, DNA size and aggressiveness

# layers	fitness value	network size	DNA size	aggrL
10	0.0180	1000	80	0.51
11	0.0336	1100	40	0.63
11	0.0596	1100	40	1.15
6	0.0703	600	40	0.83
9	0.1969	900	80	3.44
4	0.4649	400	40	3.37
3	0.6608	300	40	10.41
3	0.8930	300	40	10.60

After the evolution, the resulting population had the lamination, DNA size, aggressiveness and network size vs fitness ratios (see Table 6.1), where aggrL stands for long range aggressiveness values (the tendency to make long range connections) and fitness value is wiring cost (the smaller the better). As one can observe, the lower the aggrL value, the better the fitness value is. However, there are other factors such as

lamination and DNA size. Generally it seems better to have a large number of layers to reduce the wiring cost[51]. Since as DNA size increased, number of restrictive rules also increased, the best individual had the longest DNA.

A Multi-objective Evolutionary Test

In this final version of the model, above test was extended into a multi-objective scenario where there were two fitness values: wiring cost (lower is better) and DNA cost[52] (lower is better). As one may observe, these objectives may require a trade-off since in the previous test, the best individual had the longest DNA. This often is the nature of a multi-objective optimization problem. The modeler may require a population where there are several solutions which represent trade-offs between various objectives. Therefore this final test checked whether the multi-objective component of the model was capable of finding multiple solutions with various fitness values.

Note that the initial population members always started with small DNA sizes. Therefore, as individuals with larger DNA sizes evolved, the fitness function for the DNA size returned larger (worse) values. Yet individuals with longer DNA generally had lower wiring cost. Thus, the multi-objective optimization component was able to select individuals with lower wiring cost while still maintaining a relatively small DNA size.

In Table 6.2. below, Fitness 1 denotes DNA cost and Fitness 2 denotes wiring cost. As one may observe, decreasing DNA cost generally resulted in an increase in the wiring cost and vice versa. Another observation is that wiring cost not only depended on lamination (# layers), tendency to make long range connections (aggrL) and DNA size, but also depended on the restrictive rules themselves. Consequently individuals that had

[51]This is biologically plausible since, large brains use cortical layers to reduce the wiring cost as also discussed in subsection 5.4.1

[52]The advantage of having a smaller DNA is a smaller search space, especially for local search discussed in Modifications to DE subsection.

similar DNA size, # layers and aggrL could still have different wiring costs, since the restrictive rules encoded in their DNA were different.

Also note that while restrictive rules had some effects, aggrL and # layers strongly controlled the wiring cost outcome. Consequently, one can conclude that default or generic rules kept in the DNA is more critical than specification rules which restrict cell behavior. Therefore a mutation on these type of rules may have larger effects. However, this complies with the scale free properties of a gene regulatory network, because, while a targeted mutation in specific nodes may have critical effects, random mutations mostly keep the overall network topology intact.

Table 6.2. DNA cost and wiring cost vs lamination, DNA size and aggressiveness

# layers	Fitness 1	Fitness 2	netw size	DNA size	aggrL
2	0.0002	0.056	200	20	0.61
3	0.0004	0.028	300	40	0.59
6	0.0004	0.025	600	40	1.02
9	0.0004	0.014	900	40	1.14
9	0.0004	0.010	900	40	0.72
9	0.0004	0.0098	900	40	0.62
10	0.0004	0.0086	1000	40	0.58
10	0.0008	0.0075	1000	80	0.50

6.3 Summary and Discussion

In this chapter, a hybrid computer model that could combine the advantages of evolutionary and developmental principles was introduced. Using this model, effects of local rules on cellular differentiation, retinal mosaics, layered structures, wiring cost and network topology were explored.

Differential evolution and multi-objective optimization methods were implemented as the evolutionary component of the computer model.

There were certain modifications such as whole genome duplication and a control mechanism for crossover rate. These ideas were mostly inspired from the research on the evolution of visual system (also ideas of reusability and control of entropy that were discussed in chapter 5).

Developmental rules were inspired from the computational and developmental research on visual system. For example default Gaussian like connection scheme that depended on distance was inspired from the computational research (see Simple Cells under subsection 4.3.1). Differentiation and mosaic organization of cells were inspired from the developmental research (see subsection 3.2.3). Cell popularity was inspired from the effects of neurotrophic factors mentioned in subsections 3.1.8 and 3.1.9.

The methodology where cell specification occurred via addition of new restrictive rules was inspired from the division of labor idea describe ind subsection 2.1.3 and multiresolution idea described in subsections 5.1 to 5.3. Since whole genome duplication could occur several times, the size of the DNA and the number of restrictive rules could increase, allowing more elaborate descriptions of cell types. Since each rule was cell type specific, the DNA could contain different number of descriptive rules for each cell types. This allowed cell types with relatively generic or relatively specific behavior within the network simultaneously. Since the DNA size could increase and rules such as radius of interaction and aggressiveness were represented as floating point values, the evolutionary component was, in theory, capable of generating infinitely many number of cell types and networks of various combinations of cell types.

CHAPTER 7

7 Conclusion & Future Work

In this thesis work, both the research on disparate properties of visual system and the developmental scenarios explored by the computer model proved fruitful. Research on various perspectives revealed certain underlying principles that were discussed in chapter five. These principles, in certain ways also affected/constituted the design principles of the computer model. Therefore, the decomposition of knowledge on the visual system into its evolutionary, developmental and computational components in the second third and fourth chapters was critical.

Firstly, in chapter two, evolution of nervous system and visual system was investigated. A possible scenario for the evolutionary history of how nervous system evolved is summarized below:

1. (*Molecular phase*, skipped)
2. *Single cell phase*: creation of a *compact* toolbox for *several tasks* such as cell metabolism, cell division, chemotaxis, *phototaxis* and *action potential* (see 2.1.2)
3. *Multicellular phase I*: a more specific toolbox that builds upon the core components of the previous one, for cell-cell interactions, cell

adhesion molecules and extracellular matrix, cell collaboration and competition.

4. *Multicellular phase II*: beginning of cell specification, emergence of most primitive sensorimotor system for a multicellular organism. (For example, as discussed in section 2.1.3, simplest larvae or plankton like organisms still have *generic* cells with phototaxis. These cells can collaborate with other cells for slightly different tasks, i.e. pigmented cells exist around the cells with cilia, yet task specification is still minimal)
5. *Multicellular phase III*: refinements to cell-cell interactions, further cell specification, distinct layers of cells. Outer layer specialization for sensory tasks, motor tasks achieved by inner layer(s). Cellular communication is still slow and limited, yet it is possible that cells started to use action potentials (for electrical synapses and state change mechanisms for other etc).
6. *Synaptic phase*: emergence of first real (electrochemical) synapses. (Note that all the components were already *used* in different contexts. Action potential was used as a steering mechanism, chemical receptors were used in chemotaxis and cell collaboration).
7. Morphogenic phase: efficient usage of morphogens, cell adhesion molecules and extracellular matrix for the purposes of cellular migration and axon guidance. With the emergence of more elaborate nervous systems, reaction speeds and perception becomes a key factor for survival. (Note that growth cone like structures and cell adhesion molecules are used in both cell migration and axon guidance (subsections 3.1.2, 3.1.7). Moreover, these molecules were already mostly “discovered” in the earlier phases, since collaboration and stability were required from the start of multicellular phase, for example it is highly plausible that the transition from single cell phase to multicellular phase required cell adhesion mechanisms. Another implication is emergence of

segmented body parts, since they depend on morphogens. Segmented body parts, in developing organisms allow simple construction and then morphogenesis as well as they allow in evolving organisms separate evolution of each segment)

8. Domination phase: success of a more sophisticated nervous system and higher complexity results in the domination of other species by an urbilaterian ancestor. (This motivates researchers to seek homologies between vertebrate brains and insect *mushroom bodies*, as discussed in section 2.5)
9. *Diversification phase*: as in the transition from single celled organisms to metazoans, a compact set of toolbox is used in diverse ways.

According to this scenario, one may expect that different eye types emerged at the diversification phase, replacing the previous *eye spots.* Rhabdomeric photoreceptor cells became ganglion, amacrine and horizontal cells (see subsection 2.2.2). Eyes were used not only for circadian rhythm (there are still ancient ganglion cells in human eyes that are sensitive to the light) and detecting the luminance but also for detecting the direction of light. However, since ganglion cells were/are not sensitive to direction, this was achieved via cone cells. Some cones later evolved into rod cells and some rods and cones later evolved into bipolar cells. (Note that this does not necessarily mean linear evolution from one previous cell type to another; new combinations and slight changes in existing gene expression may more easily result in new cell types). Meanwhile, visual acuity and visual system coevolved, resulting in parallel channels for high temporal and spatial frequency resolution. Some of the mechanisms necessary for the evolution of complex organs, namely exaptation (or co-option), collage, duplication, diversification and scaffolding discussed in subsection 2.3.1, were later partly adopted by the evolutionary computer model.

In chapter three, developmental perspective revealed the connections between mechanisms such as axon guidance and cell migration.

Investigation of morphogens in subsection 3.1.2 showed that morphogens were commonly used in both migration and axon guidance. This point later lead to the realization of an underlying principle common to both evolution and development, namely the idea of reusability. The timing of events and possibility of chaotic results were also considered in this chapter. Moreover the role of external internal/stimuli were discussed. For example the investigation on the development of retina, revealed two different mechanisms to achieve regularity. In the first one, *mosaic structures* are created simply via local interactions between/within the components of cells. In the second one, mass level organization and refinement was acquired via random “waves of activations” in the retina exemplifying internal stimuli.

In the fourth chapter, a conceptual/computational perspective was employed when comparing the well known conceptual/computational modeling paradigms of the visual system, namely hierarchical, sequential and hybrid models. Mathematical models of receptive fields of the cells in retina, LGN and primary visual cortex (V1) were also investigated. Then, in the discussion section, modern view of visual system was compared to the traditional view. This showed that a traditional linear model of vision lacks a crucial component when considering the number of feedback connections and the existence of more than twelve distinct visual pathways. However, it was also apparent that the three well known traditional model (hierarchical, sequential,hybrid) constantly fed from new experiments and refined themselves. (Therefore they approach to each other and slowly converge into one single model).

Research on chapter 2, 3 and 4 stirred several questions and highlighted many directions for a deeper level investigation. In chapter 5, three of these directions were explored within a computational context. The research on the computational perspective highlighted that there were parallel information processing pathways in the visual system, this in turn lead to the question of why parallel channels evolved. This was answered by an information theoretic principle: it was a *necessity* to distribute the time-frequency information in different ratios (similar to a multiresolution

scheme) to get around the joint entropy problem. The unevenness of the P and M channel inputs to the where and what pathways and their complementary nature, was then conjectured as an indication of a similar constraint at higher levels.

The research on the evolutionary perspective lead to the idea that animals had a common “body plan” that was inherited from a common urbilaterian ancestor. This was not on the level of a primitive segmented body plan but on the level of an elaborate form where even a sophisticated nervous system existed. This in turn translated to the idea that evolving complex organisms “*reuse*“ the previous “*abstract*” components in diverse ways. A generalized version of this idea then was conjectured as: Abstract or mathematically/computationally meaningful components could maximize reusability.

The research on the developmental perspective entailed the question that how development can both have reliable and chaotic nature. This lead to the notion called edge of chaos. Ideas from researchers such as Kauffman revealed that development depends on the stable attractors and unstable/chaotic attractors that are defined in the phase space of the gene regulatory networks which are described as dynamical systems.

In the sixth chapter, some of the ideas acquired from the research on evolution and development was used as design principles to create a computer model. The computer model proved highly configurable because it allowed later additions of “new rules” which were represented as the components of DNA. Therefore new tests and approaches could build upon the previous version with ease. Moreover, evolutionary component of the model used ideas such as whole genome duplication that was drawn from the knowledge acquired during the research on the evolution of visual system. Whole genome duplication created redundancies and allowed individuals to evolve while keeping the previous progress.

Certain rules kept in the DNA (such as number of layers and the default connection scheme) may be considered more critical than specification

rules which restrict cell behavior, therefore a mutation on these type of rules may have larger effects, yet, this complies with scale free properties of a gene regulatory network, because, while a targeted mutation on a specific node may have critical effects, random mutations mostly keep the overall network topology intact.

As a conclusion, this thesis consisted of an analysis of visual system in evolutionary, developmental and computational contexts and a synthesis of the acquired data, (a synthesis that displayed the author's perspective). Development and evolution of brain was also a prominent part of the research and this affected the types of tests that were used in the computer model.

The computer model was implemented not to reverse engineer or “hard code” the literal knowledge but to apply and test some of the deep principles that were used in both the design of the computer model and in the test scenarios (that grew successively more complex). The computer model displayed a hierarchical (and *multiresolution* like) scheme where rules had different scopes (i.e. source-target specific rules vs rules that defined non-type specific default behavior).

One may draw several conclusions from this thesis, for example the question, “how can systems organize themselves in such a way that they acquire both complexity and regularity?” (which may be relevant to researchers from diverse disciplines) may be answered by the introduction of local rules that have mostly restrictive nature. Local rules reduce and control the entropy by increasing the precision of the description level of the interactions of the components in a dynamical system in a progressive way.

Another conclusion may be drawn from the complementary nature of parallel pathways in the visual system, that resulted from evolutionary constraints, that were in essence information theoretic constraints (i.e. joint entropy in 5.1). Joint entropy may explain more than simply P and M pathways (5.1.2, 5.2, 5.3). It may be possible that, where and what pathways or in more general overall segregation of information into

several “aspects” (or dimensions) was in essence a multiresolution scheme like solution to the joint entropy problem.

Future Work

In the near future, the model discussed in chapter 6 will be extended to a neural network where existing or new cell specific characteristics in the DNA are translated into different activation functions. Another possible extension is cellular migration. Current model generates and positions progenitor cells into their destinations instantly. To achieve better biological plausibility, a more realistic scenario can be applied. For example, gene regulatory networks can be used. The effects of GRNs and the edge of chaos idea to migration, differentiation and overall network topology can be explored.

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APPENDIX

Additional Formulas and Derivations for Visual System

Derivation of Retinal Ganglion Receptive Field

Assuming that light-sensitive cells are only photoreceptor cells, assuming that the role of amacrine, horizontal and bipolar cells can be reduced into synaptic weights between the photoreceptor cells and ganglion cells, receptive field (RF) of a retinal ganglion cell (RGC) traditionally formulated as following (according to Zhaoping, 2012, pp.16-21). Given x as different photoreceptor cells at different *positions*[53], a weight kernel or spatial filter $K_x(x)$ as receptive field of the ganglion cell, and a steady input image as signal $S_x(x)$, if τ is the *spontaneous firing rate*, then the output response O can be formulated as

$$O=\int K_x(x)S_x(x)dx+\tau \qquad \text{(Equation A.1)}$$

Assuming that all ganglion cells have more or less a Mexican hat receptive field, kernel function can be formulated as

$$K_x(x)=\frac{\omega_c}{\sigma_c^2}\exp[-x^2/(2\sigma_c^2)]-\frac{\omega_s}{\sigma_s^2}\exp[-x^2/(2\sigma_s^2)] \qquad \text{(Equation A.2)}$$

which is the difference of Gaussians ($\sigma_c < \sigma_s$ and $c \approx s$)[54].

[53] x does not necessarily denote a single dimension, it can be interpreted as a vector

Kernel function K and signal S also has time components. Therefore assuming a stimuli exists between t and t', the equation describing the output response becomes

$$O(t)=\int dt'dxK(x,t-t')S(x,t')+\tau \quad \text{(Equation A.3)}$$

Note that the kernel function depends on the *time interval* of input and it is now a *spatio-temporal* filter. Moreover if the stimulus is unchanging, it can be formulated as

$$S(x,t)=S_x(x)H(t) \quad \text{(Equation A.4)}$$

where S_x is the spatial filter and H(t) is step function where it is 1 if t >=0 and 0 otherwise. Assuming that the stimulus is unchanging, extending from (A.3)

$$O(t)=\int dxS_x(x)\int_0^t dt'K(x,t-t') \quad \text{(Equation A.5)}$$

Kernel function can also be extended from (A.2)

$$K(x,t)=K_t^c(t)\frac{\omega_c}{\sigma_c^2}\exp[-x^2/(2\sigma_c^2)]-K_t^s(t)\frac{\omega_s}{\sigma_s^2}\exp[-x^2/(2\sigma_s^2)] \quad \text{(Equation 4.6)}$$

where Gaussian functions are multiplied by the impulse response of center and surround components of the receptive field ($K_t^c(t),K_t^s(t)$).

Above kernel function has the expressive power to define parvocelluler (P) cells with long impulse response and small receptive fields (they have good spatial resolution) and magnocellular cells with short impulse response and large receptive field (they have good temporal resolution) (Zhaoping, 2012).

Sinusoidal gratings

A sinusoidal stimuli can be formulated as

$$S_x(x)=S_k\cos(kx+\varphi)+c \quad \text{(Equation A.7)}$$

where c is constant, φ is phase and S_k is the amplitude.

[54]Here, only center-on surround-off receptive fields will be discussed. Center-off surround-on receptive field is simply the negative of this function, $-K_x(x)$.

K_x can be decomposed into its sine and cosine components as

$$K_x(x)=\int dk\,[g_c(k)\cos(kx)+g_s(k)\sin(kx)] \quad \text{(Equation A.8)}$$

where $g_c(k)$ and $g_s(k)$ are

$$g_c(k)=\int dx K_x(x)\cos(kx),\quad g_s(k)=\int dx K_x(x)\sin(kx) \quad \text{(Equation A.9)}$$

the Fourier cosine and and Fourier sine transforms of $K_x(x)$ respectively (Zhaoping, 2012). Since the assumed $K_x(x)$ is an even function (i.e. $K_x(-x)=K_x(x)$), its Fourier sine transform $g_s(k)$ is actually 0. As a result, asymptotic response becomes

$$O(t\to\infty)=\int dx S_k[\cos(kx+\varphi)+c]\int dr\cos(rx)\int dp K_x(x)\cos(rp) \quad \text{(Equation A.10)}$$

since in essence multiplication of two cosines (sinusoidal stimuli and cosine component of $K_x(x)$) is integrated, largest response can be achieved when peaks of two cosines coincides with each other. This happens when φ is 0 and k is adjusted according to the frequency of cosine component of $K_x(x)$. As a consequence, O simply depends on

$$g_c(k)\cos(\varphi) \quad \text{(Equation A.11)}$$

Generalization

For a more general $K_x(x)$, which is not necessarily an even function $g_s(k)$ also plays a role. Thus, O depends on

$$g_c(k)\cos(\varphi)-g_x(k)\sin(\varphi)=|g(k)|\cos(\varphi-\theta) \quad \text{(Equation A.12)}$$

where g(k) is a two dimensional vector of sine and cosine components of $K_x(x)$ $g(k)=[g_c(k),-g_s(k)]^T$ having length $|g(k)|\equiv\sqrt{g_c^2(k)+g_s^2(k)}$ and angle θ.[55]

In fact, g(k) can also be interpreted as the complex variable:

$g(k)=g_c(k)-i\,g_s(k)$ and this is the Fourier transform of $K_x(x)$ at k, as given below:

[55]When θ and gs(k) both becomes 0, it falls back to the previous case where $K_x(x)$ is an even function.

$$g(k)=\int dx K_x(x)e^{-ikx}=\int dx\, K_x(x)(\cos(kx)-i\sin(kx))$$ (Equation A.13)

In the case where $K_x(x)$ is the difference of Gaussians, g(k) also depends on a difference of Gaussians in the form of

$$\omega_c \exp[-k^2\sigma_c^2/2]-\omega_s \exp[-k^2\sigma_s^2/2]$$ (Equation A.14)

where g(k) (and therefore the output response) increases with k until a peak frequency k_p then decreases symmetrically (Zhaoping, 2012, p.21).

Retinotopic Map

The approximate relationship between the input and its spatial representation on the cortical surface is given by

$$X=\lambda \ln(1+e/e_0), Y=-\frac{\lambda ea\pi}{(e_0+e)180^0}$$ (Equation A.15)

where λ and e_0 are constants, negative sign is the inversion of the image, *e is the* '*angle eccentricity*' to denote how 'peripheral' the position of stimuli (Zhaoping, 2012).

Orientation selectivity

A simple approach to model orientation selectivity could be based on the 2D Gabor connectivity function which describes the input from LGN cells to vertically oriented V1 cells (i.e. V1 cell receptive field) is defined by

$$K(x,y)=\exp[-\frac{x^2}{2\sigma_x^2}-\frac{y^2}{2\sigma_y^2}]\cos(kx+\varphi)$$ (Equation A.16)

where K(x,y) is the multiplication of a sinusoid by a Gaussian function (Teich & Qian, 2006). To a spatial grating stimulus which depends on $\cos(k'x+\varphi')$, the modeled V1 cell would respond as

$$O=\int dx\,dy\, K(x,y)S(x,y)=\int dx\,dy\, K(x,y)\cos(k'x+\varphi')$$ (Equation A.17)

where k' represents a range of frequencies centered around a specific frequency k, (Zhaoping, 2012). Moreover, in order to extend this

approach beyond vertical orientation, one can obtain kernel functions for different orientations by rotating the x, y coordinates

$$x \rightarrow x\cos(\theta) + y\sin(\theta), \quad y \rightarrow y\cos(\theta) - x\sin(\theta) \qquad \text{(Equation A.18)}$$

Motion selectivity

Motion selectivity requires the neurons to capture temporal differences. A space-time separable receptive field

$$K(x, y, t-t') = K_s(x, y)K_t(t-t') \qquad \text{(Equation A.19)}$$

where $K_s(x,y)$ is the Gabor connectivity function described in (4.20) and K_t is used for the tuning of temporal frequency of the stimuli such as a tilted grating moving in a certain direction (Zhaoping, 2012).

ODTÜ

ENFORMATİK ENSTİTÜSÜ

YAZARIN

Soyadı : Polat

Adı : Aydın Göze

Bölümü : Bilişsel Bilimler

TEZİN ADI (İngilizce) : Modeling Neurons That Can Self Organize Into Building Blocks and Hierarchies : An Exploration Based on Visual Systems

TEZİN TÜRÜ : Yüksek Lisans (X) Doktora

1) Tezimden fotokopi yapılmasına izin vermiyorum ☐

2) Tezimden dipnot gösterilmek şartıyla bir bölümünün fotokopisi alınabilir ☐

3) Kaynak gösterilmak şartıyla tezimin tamamının fotokopisi alınabilir ☐

Yazarın imzası ..... Tarih 12.09.2012