Computational Modeling of Hippocampal Neurogenesis in its Early Stages Using Branching Processes

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***Short Abstract* — Adult hippocampal neurogenesis, a process of formation of new neurons, occurs throughout life in the hippocampus, a well-known area responsible for learning and memory. The majority of the hippocampal neurogenic studies have predominantly focused on the late stages, particularly on the role of newborn neurons but little is known about its early stages that regulate the proliferation and differentiation of neural stem cells and progenitor cells to immature neurons. Based on the branching process theory and biological evidence, we develop a computational model that may represent the early-stage hippocampal neurogenic cascade. Using the model we derive the equilibrium distribution of cell population and simulate the progression of cell labeling intensity for a pulse-and-chase labeling scheme to fit into the experimental data. We adapt genetic algorithm as the parameter searching heuristic in the preliminary study. Our model together with simulation results reveal unknown but meaningful biological parameters, such as apoptotic rate at each stage, etc. and allow us to modulate overall efficiency of hippocampal neurogenesis in both normal and diseased conditions with perturbations.**

***Keywords* — hippocampal neurogenesis, cell labeling, homeostasis, computational modeling, Branching Processes, simulation, apoptosis**

I. Introduction

Until recently, neurogenesis was thought to be restricted to the embryonic development. However, it is now known that it persists in the adult hippocampus of rodents and humans [1], where it has been shown to be involved in learning and memory formation [2].

The majority of the studies have predominantly focused on the late stages of neurogenesis, particularly on the role of newborn neuron, while little is known about the early stages, such as the molecular and cellular mechanisms that mediate the proliferation and differentiation of neural stem cells to immature neurons [3]. Based on the branching process theory [4], we develop a computational model which can reliably and efficiently test biological scenario that affect early stages of neurogenic cascade. Simulation can identify unknown but critical biological parameters, such as cell cycle durations and apoptotic rates. In addition, our computational model allows us to predict how perturbation would affect neurogenic homeostasis.

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II. Methods

When studying neurogenesis, BrdU (Bromodeoxyuridine) is injected into mice and gets incorporated in to proliferating DNA. Over the course of the neurogenesis, BrdU can be traced in cells that are the lineage of the initial proliferating cells. The fate of each initial proliferating cell may be: proliferation (becomes an ANP - amplifying neural progenitor), differentiation (NB - neuroblast or IN - immature neuron) and cell death by apoptosis.

We build a stochastic model using Branching Processes to represent the neurogenesis cascade and aim to estimate apoptotic rates at all stages, distributions cell type durations and renewal probability of ANP. We used published data for total BrdU+ cells [5] and acquired partial BrdU+ cells for all cell types. Experimentally, this is a challenge because there are no markers that can absolutely differentiate late ANP and early NB. Therefore, we have two scenarios, where in scenario 1 we assume that ANP staining is specific while NB is not, and vice versa in scenario 2.

III. Conclusion

Fitting simulation results to experimental data in both scenarios it agrees on that (1) apoptotic rates are high (> 60%) at the end of both NB and IN stages and low (< 5%) at the end of S and G2M phases of ANP cells; (2) renewal probability of ANP is relatively low (< 20%); (3) expected duration for NBs is ~ 200 hrs with high variance in exact durations; (4) expected duration for apoptotic cells is 1.5 hrs; and (5) maximum number of possible divisions of ANP is between 1-5 times.

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