Quantitative modeling of the dynamics of adult hippocampal neurogenesis in mice

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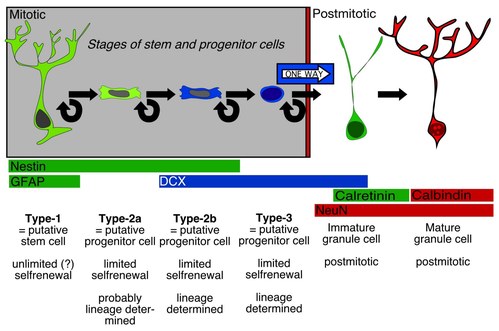
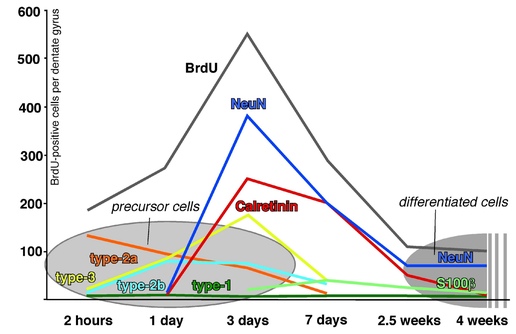
335

Introduction

Neurogenesis refers to the generation of new neurons in the brain. We are interested in the dynamics of **adult neurogenesis** in the **dentate gyrus** of the hippocampus, which is special in that it generates new neurons throughout life. The hippocampus has been associated with a variety of functions, in particular episodic memory.

During adult hippocampal neurogenesis newly generated granule cells pass through different stages. In 2004 we have proposed a kinetic model of this development, but the exact dynamics of neuronal development in the dentate gyrus was still unknown and a few contradictions remained. (Kempermann et al., TINS, 2004)
Based on new experiments we now built a refined mathematical model of hippocampal neurogenesis in adult mice.

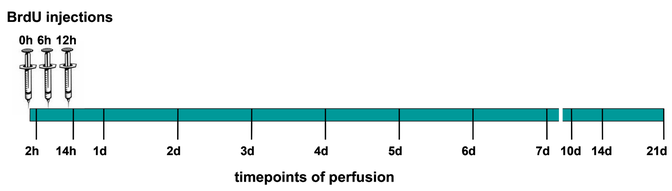




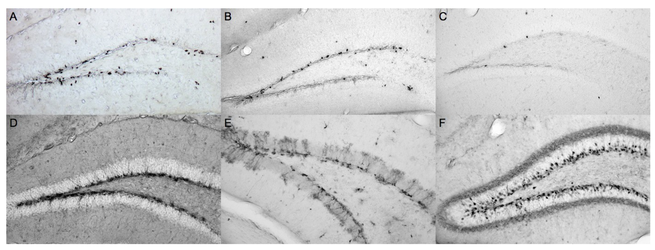
Methods

Animal experiments:

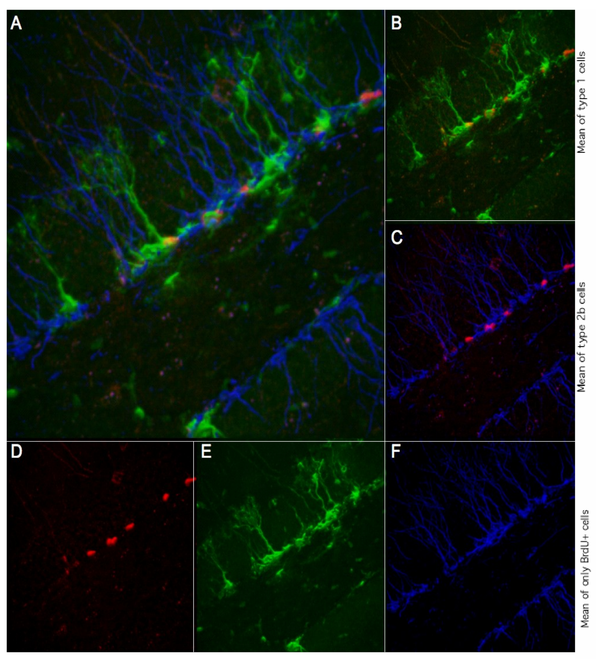
- Animals: 85 NestinGFP (based on C57BL6) mice, n=5-7 per group (2-4♂ and 2-4♀), 6 - 8.5 weeks old
- 3 i.p. injections of 50mg/kg bodyweight, 1 injection every six hours (8 am, 2 pm, 8 pm)
- Determination of the absolute number of BrdU-positive, GFP-positive, DCX-positive and calretinin-positive cells
- Analysis of the relative number of cells in the different developmental stages



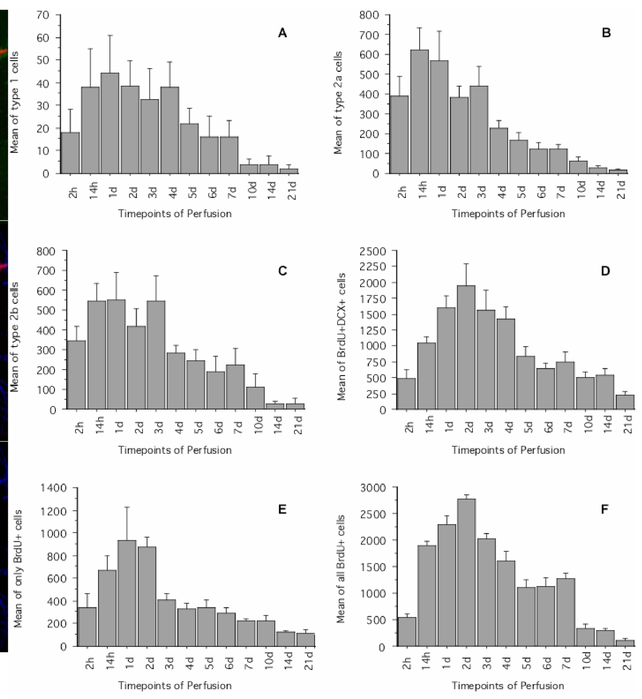
Biological Results



A,B,C: BrdU **A**: after 1 day; **B**: after 6 days; **C**: after 21 days ; **D**: DCX (doublecortin); **E**: Nestin-GFP, cells with process are classified as type 1 cells, without process as type 2 cells; **F**: staining for Calretinin, identification of early postmitotic cells



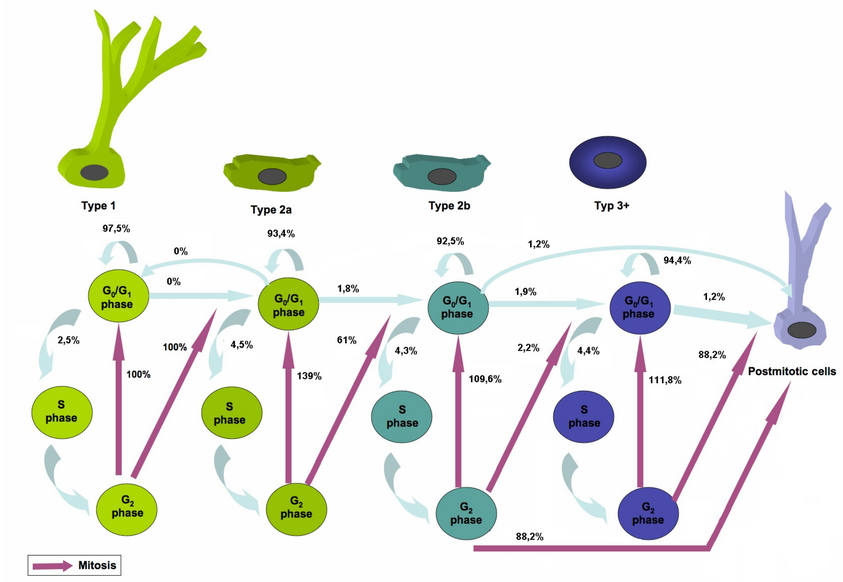
BrdU (red), NestinGFP (green) and DCX (blue)
A: merged, **B**: BrdU and Nestin-GFP, **C**: BrdU and DCX
D: BrdU, **E**: Nestin-GFP, **F**: DCX



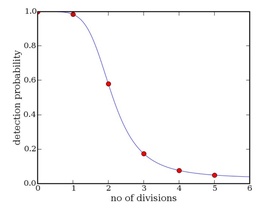
Number of cells at different developmental stages at different timepoints after BrdU
A: Type 1, **B**: Type 2a, **C**: Type 2b, **D**: Type 3+,
E: Unknown, **F**: BrdU total

Mathematical Modeling

For modeling the dynamics of neurogenesis we used an extended version of the kinetic model. Based on the idea of Leslie matrices we built a computational model (discrete and linear) with additional states representing the cell cycle for each mitotic cell type.
Additional assumptions based on the biological knowledge are:
S-phase length: 8h
Cell cycle length: >20h
BrdU availability after injection: 2h

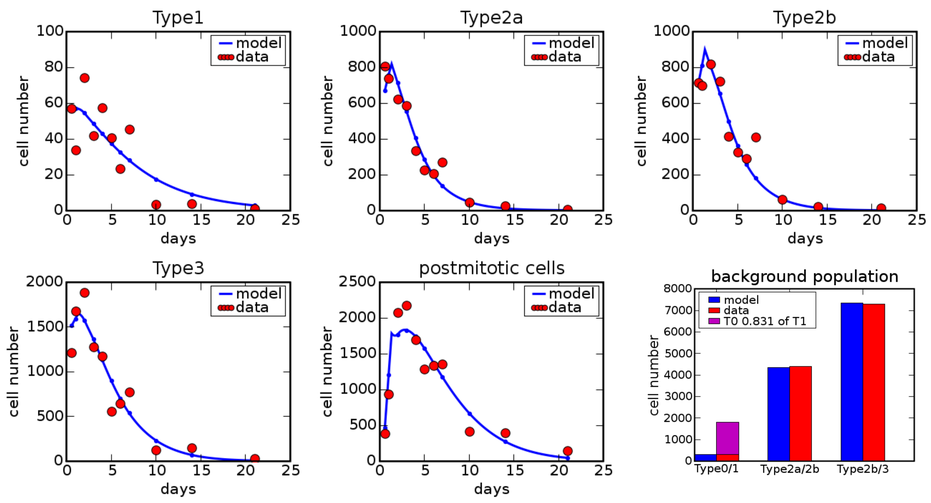


Additionally, we included a self-consistent labeling process and different dilution scenarios. The most realistic scenario leading to good results is the approximation by a sigmoidal detectability function. Furthermore we performed an analysis of the steady-state background population of unlabeled cells based on the eigenvectors of the transition matrix.
All calculations and simulations were performed with *Python*.



Results

The results of the model match the data well. Additionally, based on the eigenvectors of the transition matrix we derive an estimate for the population of unlabeled cells, which matches the experimental data well without being fitted to them.



Summary

Based on the earlier model we performed new experiments, which generated an extensive amount of data. We have established a dynamic model of neurogenesis in the hippocampus of adult mice, which fits the experimental data well. This model enables us to deduce division rates, properties of the labeling process and certain properties of cell populations. In addition we plan to do a sensitivity analysis of the solution, which will give information about the importance of single parameters or combinations of certain parameters.

Furthermore, the model allows to connect and compare different studies. It is a first step towards the modeling of a regulated process, for example in mice living in an enriched environment or with physical exercise. The goal would be to determine the parameters that are changed compared to baseline conditions in order to define the points of regulation.