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From Mouse to Human, What Can Mathematical Modelling Tell us About the Evolution of Cortical Development?

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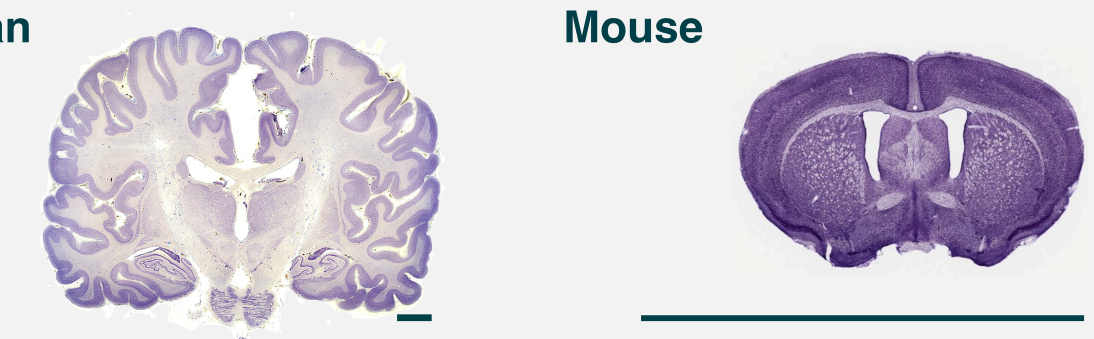
1. Background

The mammalian cerebral neocortex has a unique structure, composed of layers of different neuron types, interconnected in a stereotyped fashion. The radial thickness of the cortex is roughly preserved across species, while the most striking differences consist of final neuronal output and surface area. The latter accounts for a 1000-fold variation, when comparing mouse to human, resulting into a remarkable increase of cortical function. However the overall developmental program that gives rise to each of these cortices seems to be conserved.

1 cm

Human **Mouse**



Figures adapted from DeFelipe, *Front. Neuroanat.* 2011

Among the many factors determining the specific development of a normal cortex in mammalian species are: the size of the founder population present at the beginning of cortical neurogenesis, the length of neurogenesis, the proportion of different cortical progenitor types, and the fine-tuned balance between self-renewing and differentiative divisions.

Our goal is to integrate mathematical modelling and experimental observations to highlight the divergent factors that can explain cortical diversity amongst mammalian species.

2. The Mathematical Model of Neurogenesis

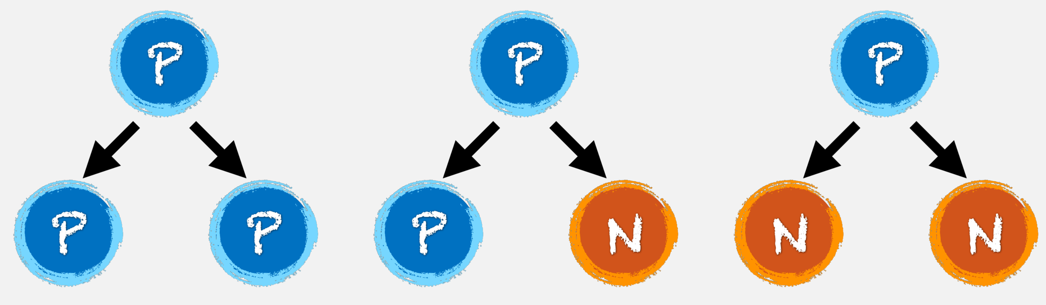
We define a simple model of neurogenesis, describing the dynamics of proliferation and differentiation.

Cell populations:

P — Progenitors including all pre-mitotic cell types involved in neocortex development, e.g.neural progenitor cells, inner and outer radial glia, intermediate progenitors.

N — Neurons: postmitotic and permanent (no migration nor death is modelled).

Modes of Division:



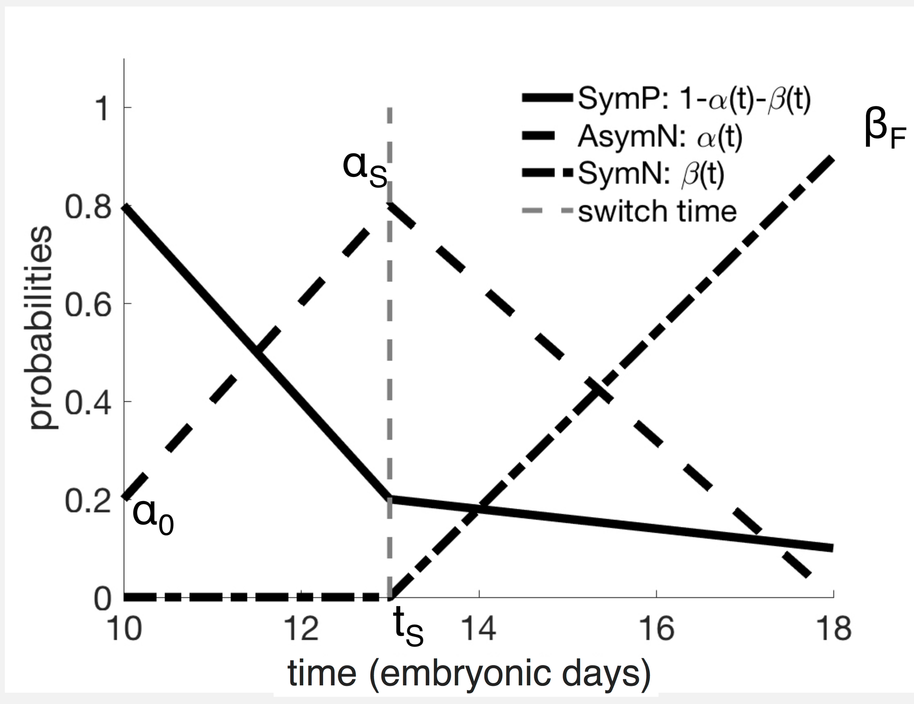
Time-dependent probabilities describe the preferred mode of division in the course of neurogenesis. Four parameters determine the shape of these functions, hence the trajectory in parameter space:

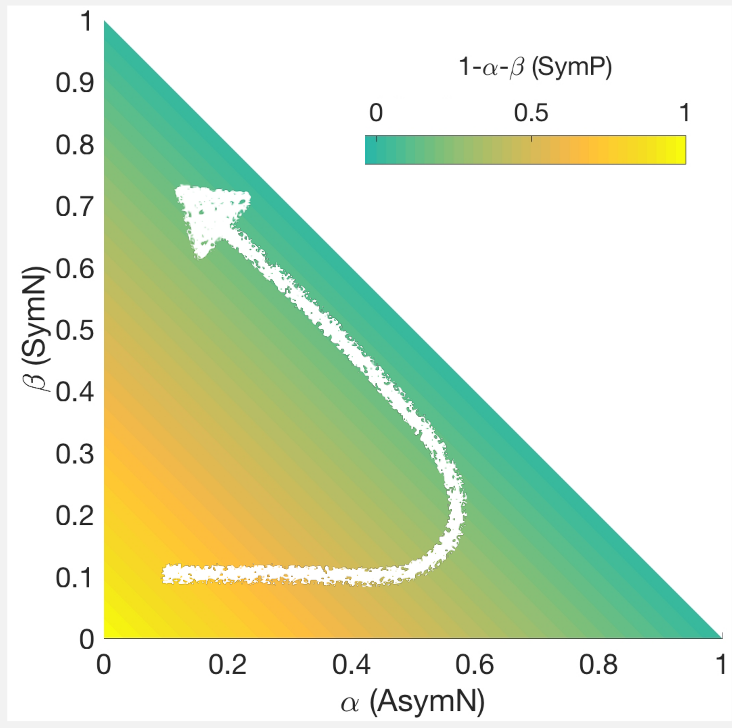
α_0: proportion of AsymN at onset of neurogenesis

α_S: proportion of AsymN at time of strategy switch

β_F: proportion of SymN at end of neurogenesis

t_S: time of switch to a strategy favouring SymN.





1000
fold increase in surface area from mouse to human [1]

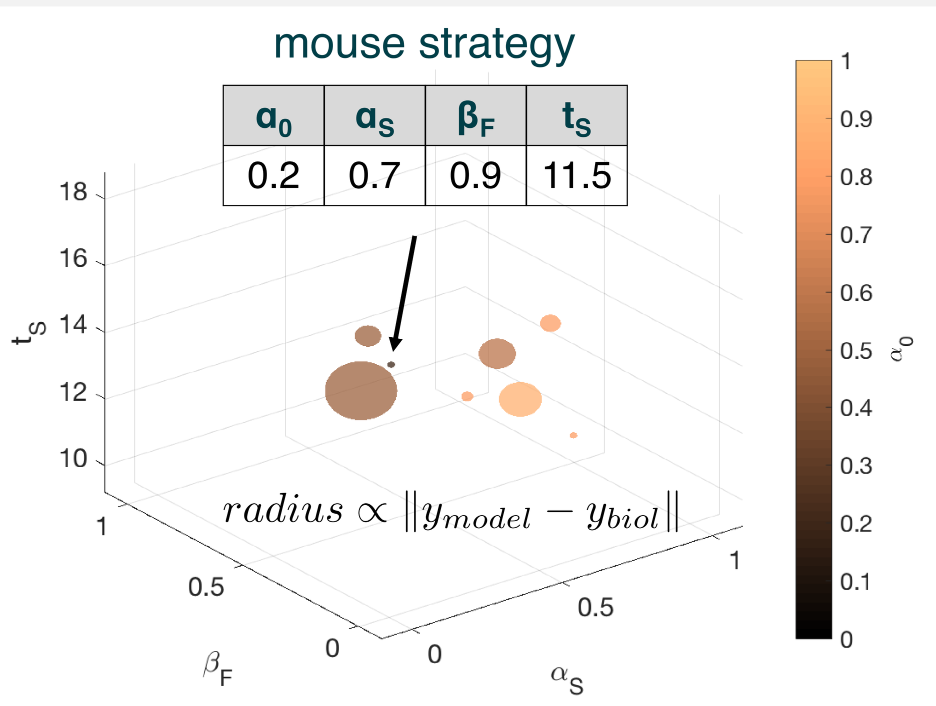
12 Milion vs 21 Billion
neocortex neurons (mouse vs human) [2]

8 days vs 85 days
neurogenesis length (mouse vs human) [3]

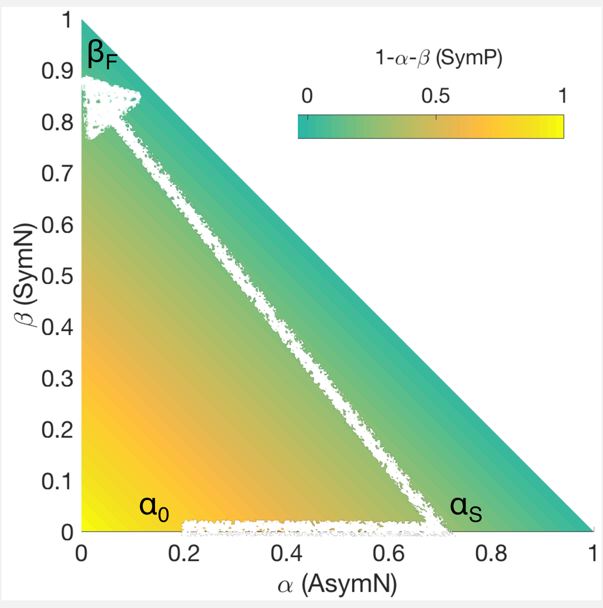
3. The Strategy to Build a Mouse Neocortex

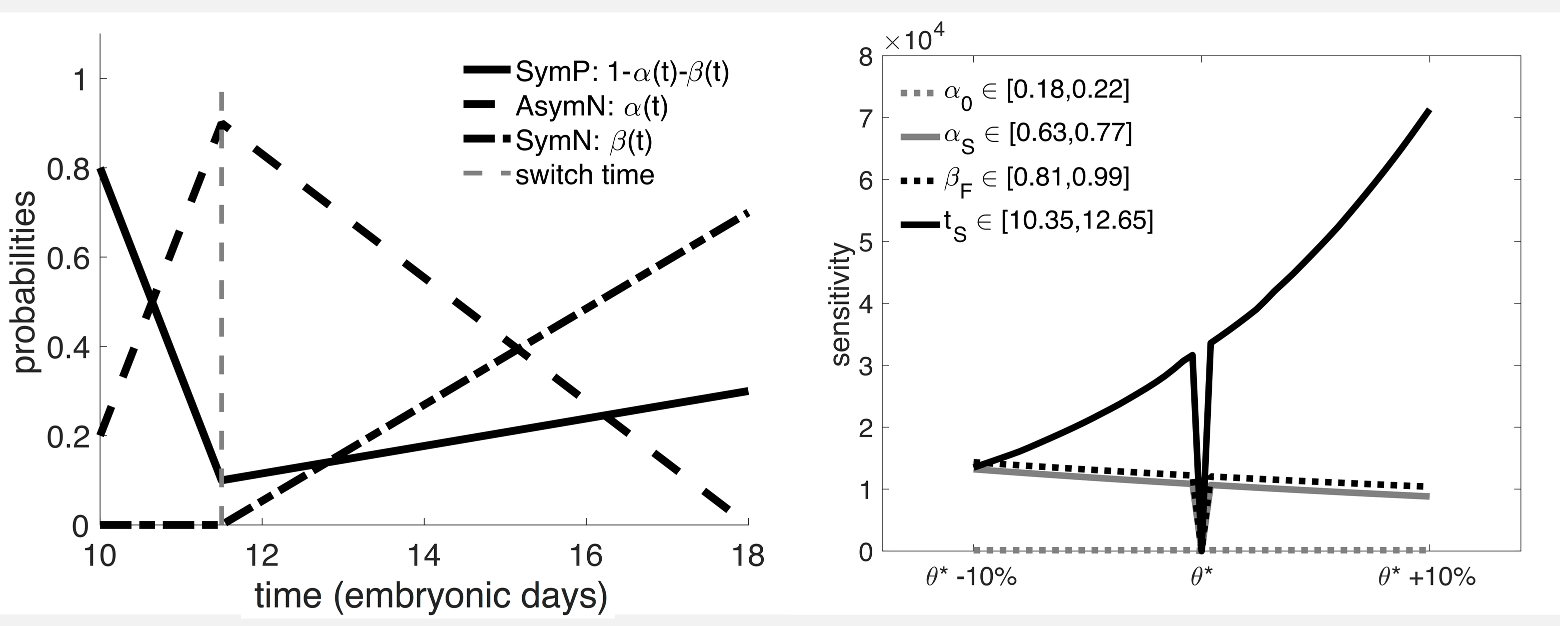
The model allows systematic exploration of the strategy space by simultaneously varying all parameter values within biologically relevant ranges to find the strategy (strategies) matching the observed outcomes:

- **Half Neuronal Production by Mid-neurogenesis**
- **Final neuronal output ~ 40 x Founder Progenitors**



α_0	α_S	β_F	t_S
0.2	0.7	0.9	11.5



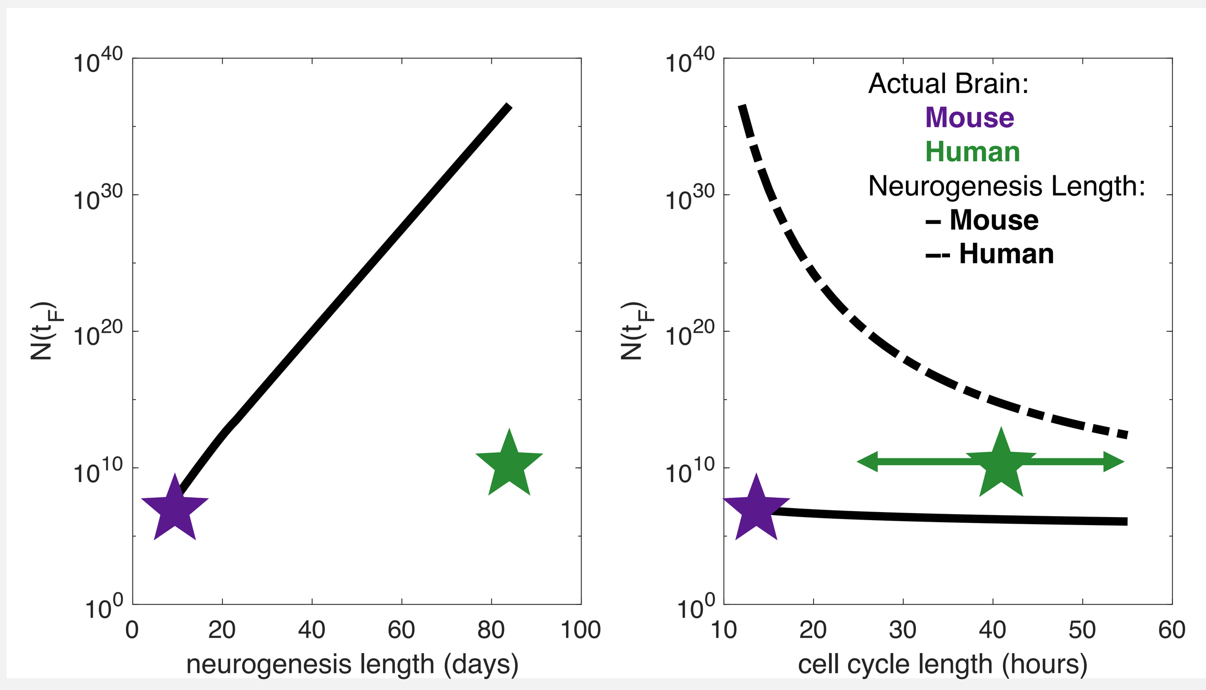


Parameter sensitivity and uncertainty quantification studies reveal that the highest sensitivity of the output can be attributed to variations in the t_S parameter.

4. From Mouse To Human: How Does Neuronal Output Scale?

Our model predicts that, compared to the actual human neocortex:

- A mouse neocortex with human neurogenesis duration would have 10^{26} times more neurons.
- Mouse neurogenesis with human cell cycle length would produce 1.6×10^4 times less neurons.
- Mouse neurogenesis with human cell cycle and neurogenesis length would produce 3×10^4 more neurons.



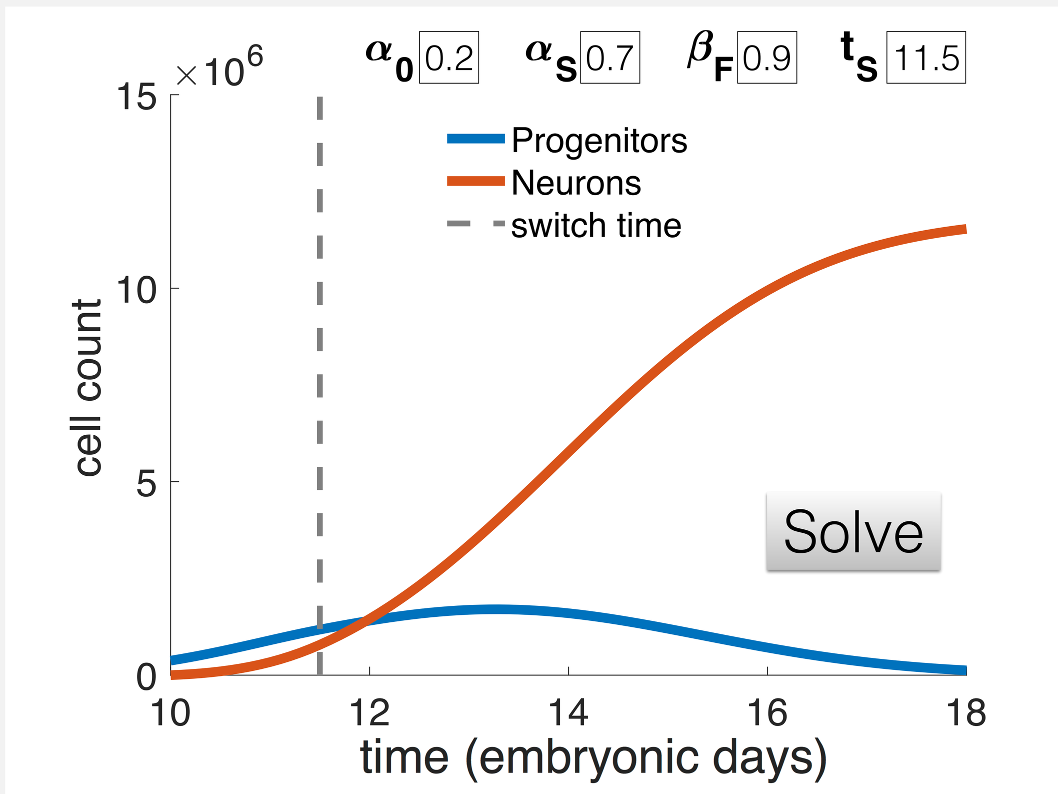
Hence our mouse model predicts that changes in neurogenesis duration, cell cycle length and size of founder population are not sufficient to explain actual human neuronal output.

5. The Neurogenesis Simulator

We have developed a graphic user interface allowing to select and calibrate the neurogenesis model, observing how the temporal dynamics vary when changing parameter values.

The user can select and compare strategies of neocortical development across different species.

In the long term we envisage the use of our neurogenesis model to map multiple species trajectories on the strategy space to highlight the paths of evolution.



References and Funding

This research is funded by St John's College Research Centre, St John's College, Oxford.

For more information on the neurogenesis simulator: www.dpag.ox.ac.uk/team/noemi-picco Email: picco@maths.ox.ac.uk

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