A mathematical model of cortical neurogenesis combined with experimental data

50 ans du LJLL

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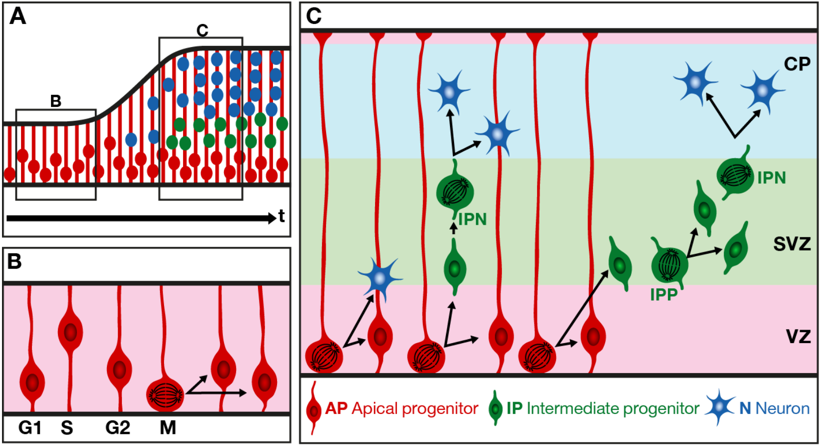
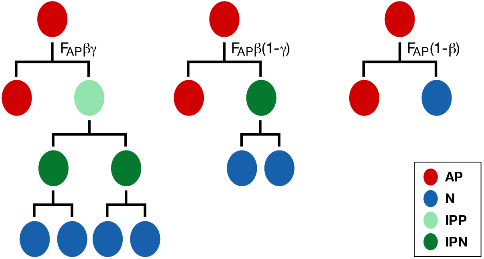
Neurogenesis in the mouse cerebral cortex



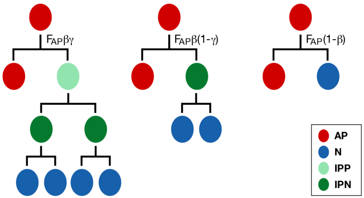
AP and IP divisions

Complex and dynamic cell population with time dependent features (cell cycle parameters, type of division)



- Earlier models (with quantitative data) considering all progenitor types together (Caviness, 1995)
- Experimental cell cycle parameters with AP, IPP, and IPN distinction (Arai, 2011)
- Mathematical model without data calibration (Freret-Hodara, 2016)

Compartmental or Stochastic model

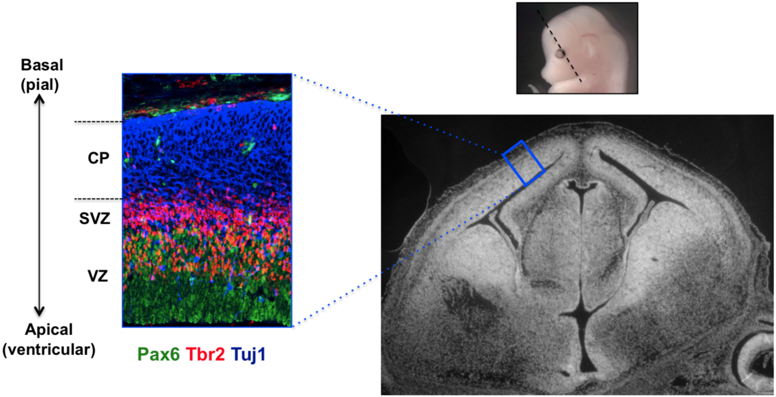


n	division	flux
1	$AP \to 2AP$	$k_1 AP$
2	$AP \to AP + N$	$k_2 AP$
3	$AP \to AP + IPP$	$k_3 AP$
4	$AP \to AP + IPN$	$k_4 AP$
5	$IPP \to 2IPN$	$k_5 IPP$
6	$IPN \to 2N$	$k_6 IPN$

$$\frac{d}{dt}\begin{pmatrix} AP(t) \\ IPP(t) \\ IPN(t) \\ N(t) \end{pmatrix} = \begin{pmatrix} k_1 & 0 & 0 & 0 \\ k_3 & -k_5 & 0 & 0 \\ k_4 & 2k_5 & 0 & 0 \\ k_2 & 0 & 2k_6 & 0 \end{pmatrix} \begin{pmatrix} AP(t) \\ IPP(t) \\ IPN(t) \\ N(t) \end{pmatrix}$$

Experimental setup

Neurogenesis in the cerebral cortex of E14.5 mouse embryos.

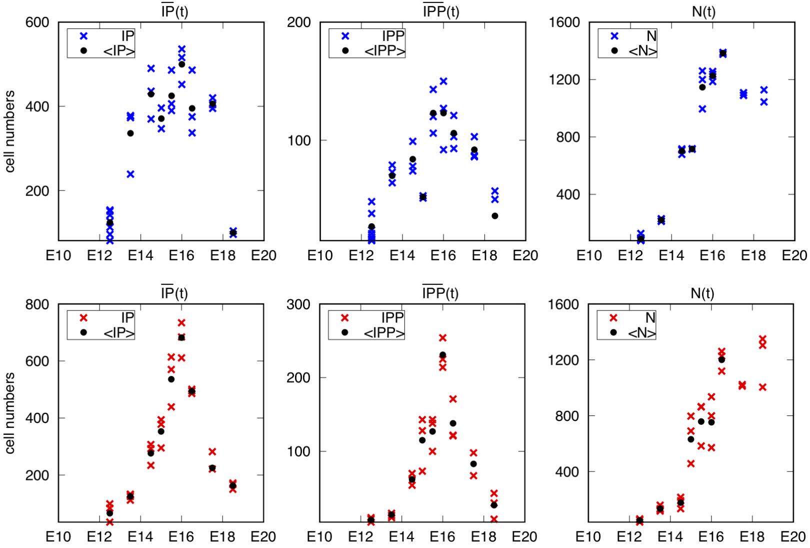


Pax6+ cells: Apical progenitors (APs)

Tbr2+ cells: Basal progenitors = Intermediate progenitors (IPs) Pax6+ Tbr2+ (IPP)

Tuj1+ cells: Neurons (N)

Datasets used to calibrate the model



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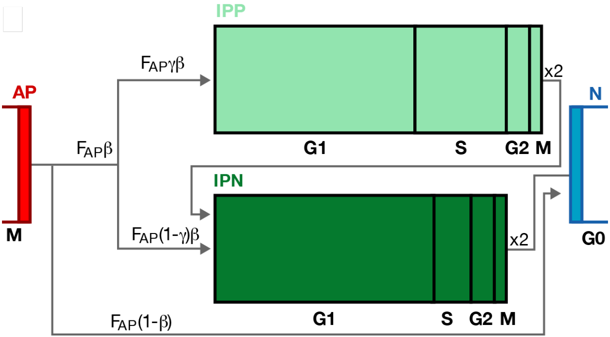
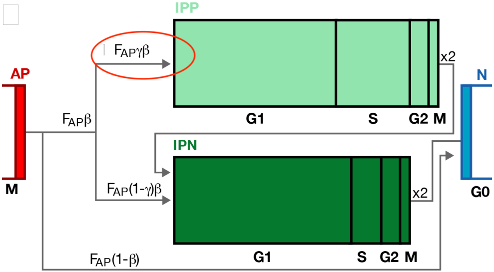
Mathematical model



Inputs:	Two scales:	Outputs:
$F_{AP}(t)$	time t	$IPN(t,a)$
$\beta(t)$	age $a \in [0, T_c]$	$IPP(t,a)$
$\gamma(t)$	in the cell cycle	$N(t)$

Multiscale mathematical model



Micro scale: cell kinetics in the cell cycle

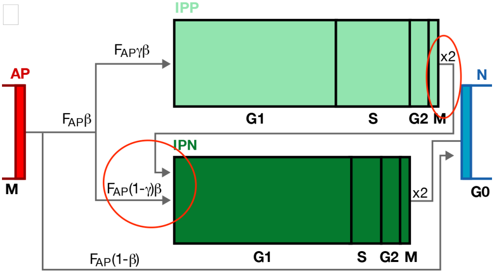
Transport PDEs

$$\partial_t IPP(t,a)+\partial_a IPP(t,a)=0,\ \ a\in[0,T_c^{IPP}]$$
$$\partial_t IPN(t,a)+\partial_a IPN(t,a)=0,\ \ a\in[0,T_c^{IPN}]$$

Flux conditions between cell compartments at $a=0$

$$IPP(t,a=0)=\gamma(t)\beta(t)F_{AP}(t)$$
$$IPN(t,a=0)=2IPP(t,a=T_c^{IPP})+(1-\gamma(t))\beta(t)F_{AP}(t)$$

Multiscale mathematical model



Micro scale: cell kinetics in the cell cycle

Transport PDEs

$$\partial_t IPP(t,a) + \partial_a IPP(t,a) = 0, \quad a \in [0, T_c^{IPP}]$$

$$\partial_t IPN(t,a) + \partial_a IPN(t,a) = 0, \quad a \in [0, T_c^{IPN}]$$

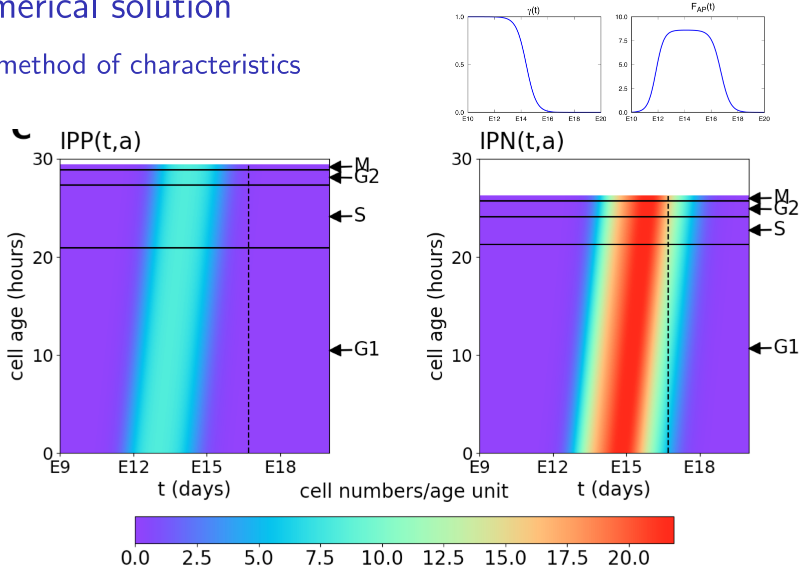
Flux conditions between cell compartments at $a = 0$

$$IPP(t, a = 0) = \gamma(t)\beta(t)F_{AP}(t)$$

$$IPN(t, a = 0) = 2IPP(t, a = T_c^{IPP}) + (1 - \gamma(t))\beta(t)F_{AP}(t)$$

Numerical solution

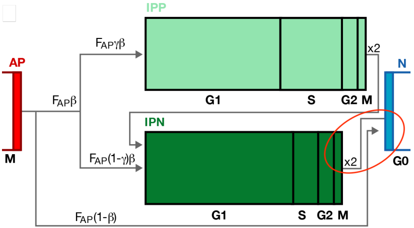
method of characteristics



Outputs / observables macro scale

- Integration in time of mitotic IPNs and neurogenic AP

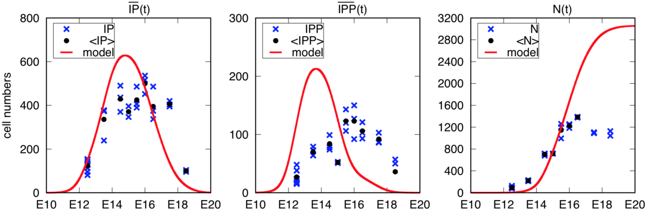
$$N(t) = \int_0^t \left((1-\beta(s))F_{AP}(s) + 2IPN(s, a = T_c^{IPN})\right) ds$$



- Integration in age over full cell cycle: total cell counts

$$\begin{cases} \overline{IPP}(t) = \int_0^{T_c^{IPP}} IPP(t,a)da \\ \overline{IPN}(t) = \int_0^{T_c^{IPN}} IPN(t,a)da \end{cases} \qquad \overline{IP}(t) = \overline{IPP}(t) + \overline{IPN}(t)$$

Multi objective optimisation



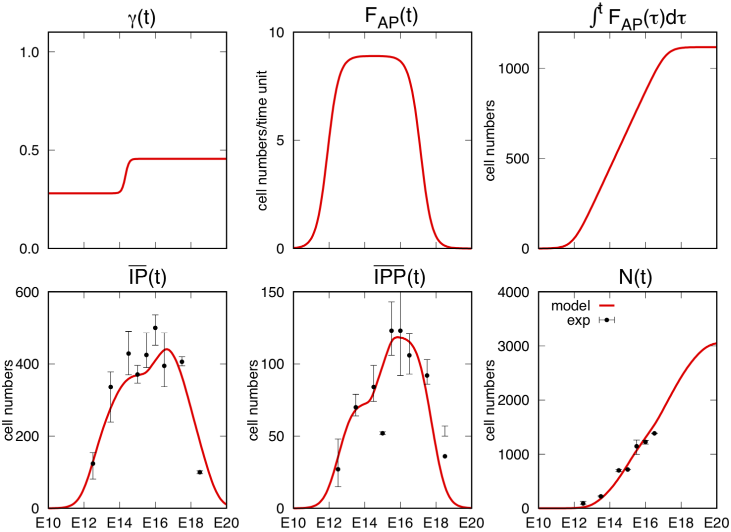
$$J(p) = \sum_{X \in \{IP, IPP, N\}} \frac{(J_X(p) - J_X^\star)^2}{(J_X^{\max} - J_X^\star)^2}$$

where

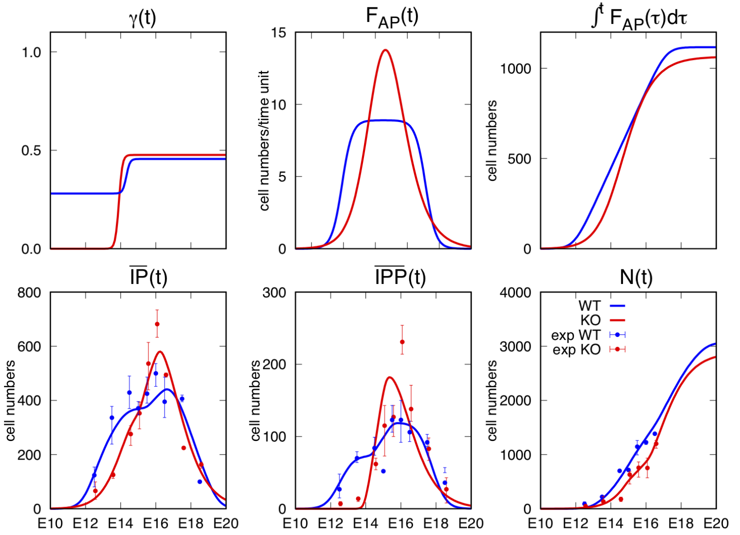
$$J_X(p) = \sum_{i=1}^{N_{exp}} w_i^X (\overline{X}(t_i, p) - X_i^{exp})^2$$

$$\mathcal{P} = \{p = (K_{AP}, s_+, t_+, s_-, t_-, \gamma_0, \gamma_1, s_\gamma, t_\gamma),$$
$$p_i \in [p_{\min}^i, p_{\max}^i], i = 1, \ldots, 9\}. \quad \Rightarrow$$

Control data calibration



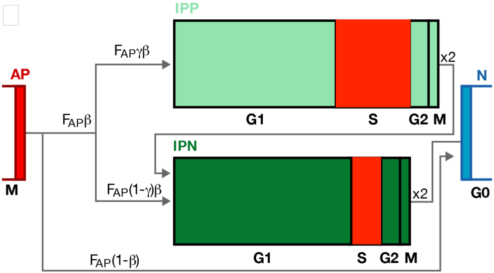
Control versus mutant



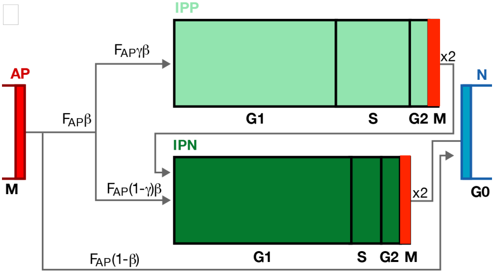
Outputs / observables meso scale : partial cell counts

Integration in age over phase S : labelling index

$$\begin{cases} \overline{IPP}_S(t) = \int_{T_{G1}^{IPP}}^{T_{G1}^{IPP}+T_S^{IPP}} IPP(t,a)da \\ \overline{IPN}_S(t) = \int_{T_{G1}^{IPN}}^{T_{G1}^{IPN}+T_S^{IPN}} IPN(t,a)da \end{cases} \quad LI(t) = \frac{\overline{IPP}_S(t) + \overline{IPN}_S(t)}{\overline{IP}(t)}$$



Outputs / observables meso scale : partial cell counts



Integration in age over phase M : mitotic index

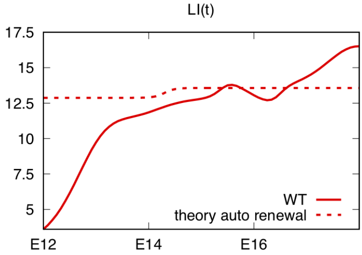
$$\begin{cases} \overline{IPP}_M(t) = \int_{T_c^{IPP}-T_M^{IPP}}^{T_c^{IPP}} IPP(t,a)da \\ \overline{IPN}_M(t) = \int_{T_c^{IPN}-T_M^{IPN}}^{T_c^{IPN}} IPN(t,a)da \end{cases} \qquad MI(t) = \frac{\overline{IPP}_M(t) + \overline{IPN}_M(t)}{\overline{IP}(t)}$$

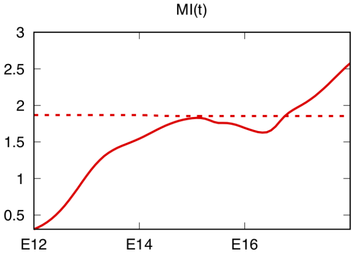
Labeling and mitotic indexes

$$LI(t) = \frac{\overline{IPP}_S(t) + \overline{IPN}_S(t)}{\overline{IP}(t)} \quad MI(t) = \frac{\overline{IPP}_M(t) + \overline{IPN}_M(t)}{\overline{IP}(t)}$$

Steady state auto renewal regime

$$LI = \frac{T_S}{T_c} \qquad MI = \frac{T_M}{T_c}$$





Conclusions

- The model can be calibrated on control and mutant datasets
- Observed neuron count delay in mutant at E14 is explained
- Meso scale model outputs provide additional info difficult to access experimentally
- Online demo and parameter testing available on github : cemone

Thank you for your attention !