Cell dynamics during the development of the cerebral cortex

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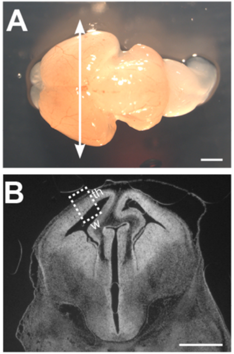
Probability meets Biology July 2026

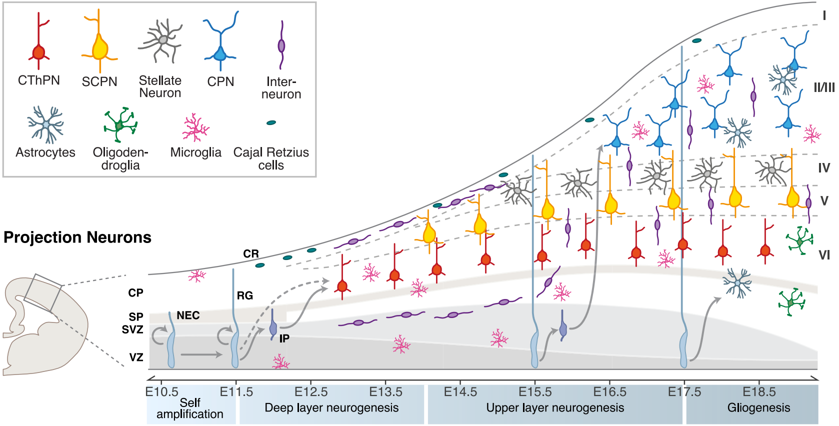
Joint work

- A stochastic model for neural progenitor dynamics in the mouse cerebral cortex, *Math Biosci* 2024, with Jules Olayé
- A multiscale mathematical model of cell dynamics during neurogenesis in the mouse cerebral cortex, *BMC Bioinfo* 2019
  with Marie Postel, and wet biology collaborators Alice Karam, Guillaume Pézeron, Sylvie Schneider-Maunoury

Biological background and deterministic model

Biological background: cortical neurogenesis in rodents

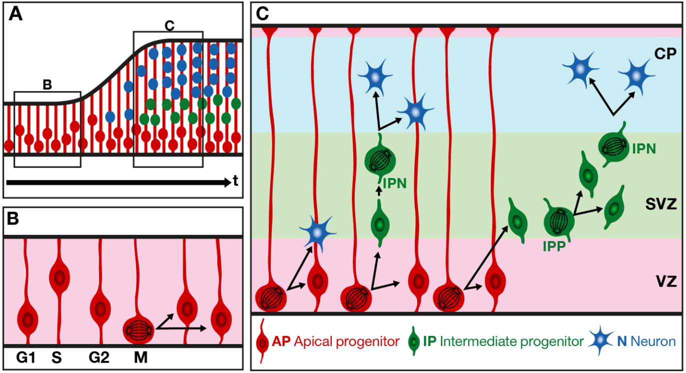




Di Bella Neuron 2024

Biological background: cortical neurogenesis in rodents

Pyramidal (excitatory projection) neurons



Biological background: cortical neurogenesis in rodents

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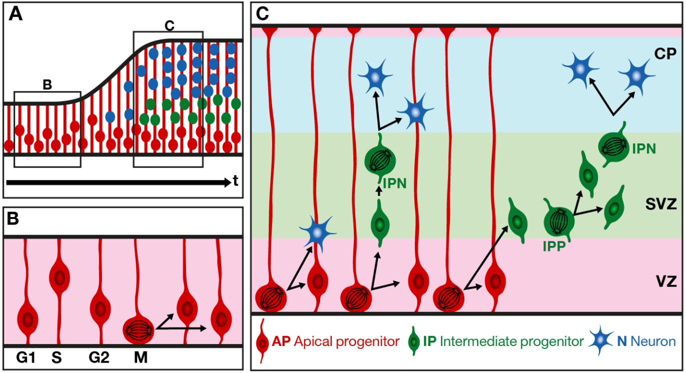
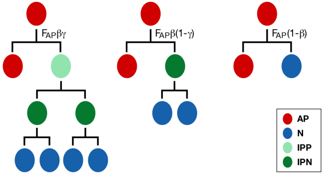


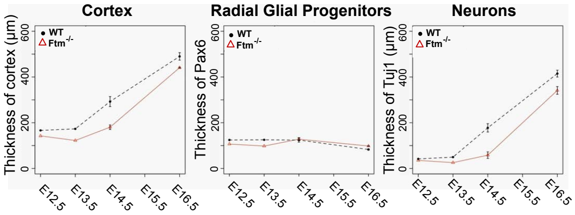


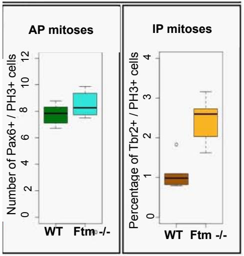
- Pyramidal (excitatory) neuron pool
- Neurogenesis time window E11-E17
- Neuron layering (apical towards basal side)
- Neuronal yield associated with intermediate progenitors

Motivation and positioning

Disruptions of brain development associated with defects in the primary cilium

- Mouse model of human ciliopathies (Ftm-/- mutation)
- Subtle alterations in corticogenesis
  - Transient decrease in the cortical thickness (SVZ and neuronal layer) compensated for at the end of neurogenesis
  - Apparent increase in the number of mitotic and S-labeled IP at mid-neurogenesis





$\Rightarrow$ **Investigation of IP dynamics**

Motivation and positioning

Disruptions of brain development associated with defects in the primary cilium

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Design of an appropriate modeling framework

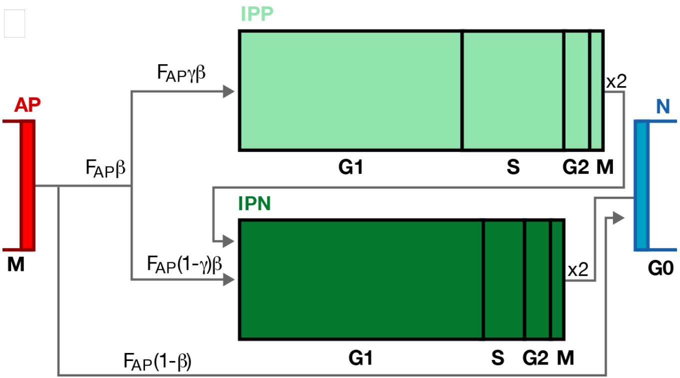
accounting for

- Different progenitor types
- Cell distribution within the cell cycle phases
- Quantitative assessment of cell numbers

Interdisciplinary NeuroMathMod project

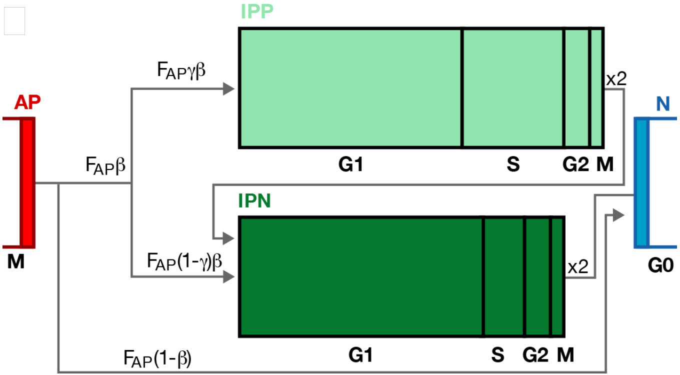
Sorbonne Université Emergence Call

Macroscopic level: compartmental dynamics



$AP(t)$	Apical Progenitors	$F_{AP}(t)$	AP commitment rate
$IPP(t)$	Proliferative Intermediary Progenitors	$1-\beta(t)$	direct neurogenesis rate
$IPN(t)$	Neurogenic Intermediary Progenitors	$\beta(t)$	indirect neurogenesis rate
$N(t)$	(post-mitotic) Neurons	$\gamma(t)$	balance IPP/IPN from APs

Microscopic level : progression along the cell cycle



Focus on the IP dynamics

IP population structured according to the cytologic age a

$\Rightarrow$Transport equations

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

Microscopic level : progression along the cell cycle

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

$$\begin{aligned} T_C^{IPP} &= T_{G1}^{IPP} + T_S^{IPP} + T_{G2}^{IPP} + T_M^{IPP} \\ T_C^{IPN} &= T_{G1}^{IPN} + T_S^{IPN} + T_{G2}^{IPN} + T_M^{IPN} \end{aligned}$$

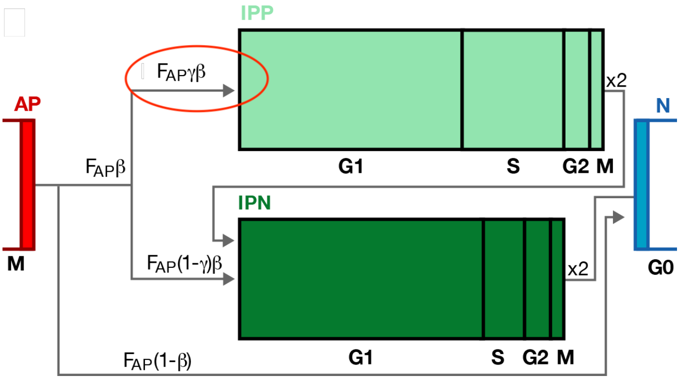
Recovery of IP macroscopic cell numbers

Integration in age over the whole cell cycle

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

Connection micro/macro: IP inflows and outflows

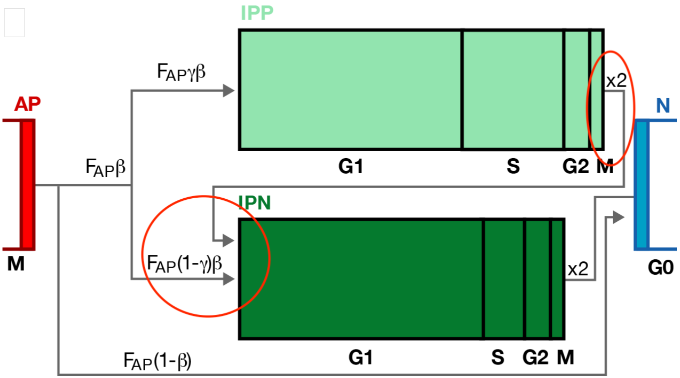
Inflow into the IPP compartment: contribution of AP divisions



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

Connection micro/macro: IP inflows and outflows

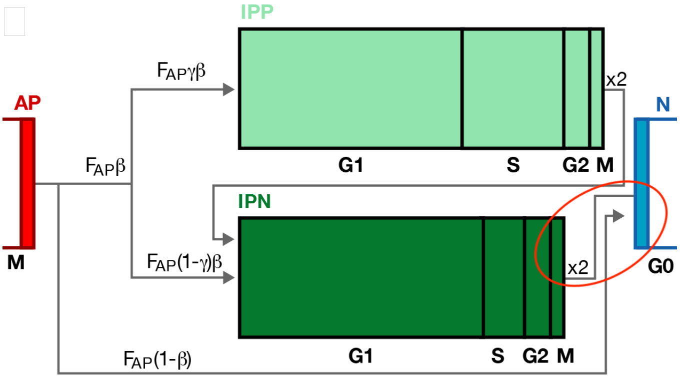
Inflow into the IPN compartment: contribution of AP and IPP divisions



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

Connection micro/macro: IP inflows and outflows

Exflow from the IPN compartment: contribution to indirect neurogenesis



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

Connection micro/macro: IP inflows and outflows

Model summary

PDE transport equations

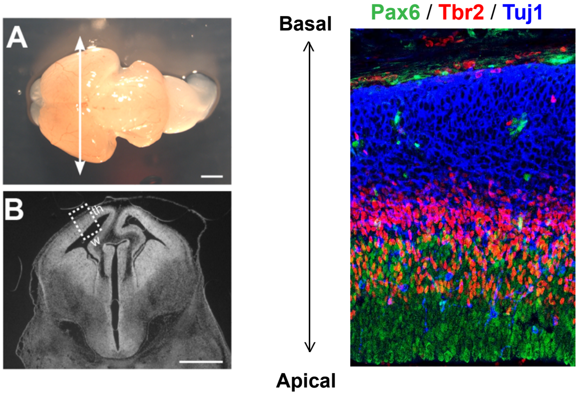
$$\begin{cases} \partial_t IPP(t,a) + \partial_a IPP(t,a) = 0, & t > t_0,\ a \in]0, T_C^{IPP}[\\ IPP(t_0,a) = IPP_0(a), & \end{cases}$$

Boundary conditions

$$\begin{cases} \partial_t IPN(t,a) + \partial_a IPN(t,a) = 0, & t > t_0,\ a \in]0, T_C^{IPN}[\\ IPN(t_0,a) = IPN_0(a), & \end{cases}$$

$$\begin{aligned} IPP(t,a=0) &= \gamma(t)\beta(t)F_{AP}(t) \\ IPN(t,a=0) &= (1-\gamma(t))\beta(t)F_{AP}(t) + 2IPP(t,a=T_C^{IPP}) \\ \frac{dN}{dt}(t) &= (1-\beta(t))F_{AP}(t) + 2IPN(t,a=T_C^{IPN}). \end{aligned}$$

Initial conditions : empty IP and N compartments



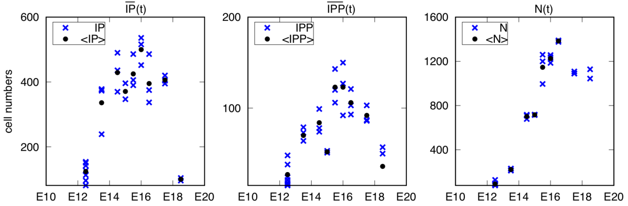
Identification of progenitors
AP **Pax6**, IP **Tbr2**
IPP **Pax6Tbr2**
and neurons **Tuj1**

Huge experimental work
- Immunofluorescence staining
- Cell counting on 2D slices

Yet . . .
- Small datasets
- Low time sampling rate

Multi-criterion objective function

- 3 **different datasets** : IP, IPP and N, with clear **differences in amplitude range** ($\times 5$)
- in **CTL** or **KO** situation
- Too **few replicates** to weight by empirical variance
- Varying sampling rate



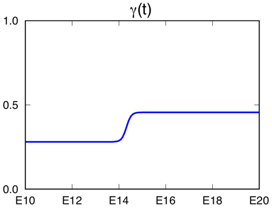
Dataset-specific criterion $$J_X(p) = \sum_{i=1}^{N_{exp}} w_i^X (\overline{X}(t_i, p) - X_i^{exp})^2$$

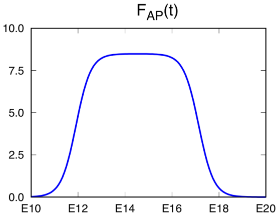
Global criterion $$J(p) = \sum_{X \in \{IP, IPP, N\}} C_X \frac{(J_X(p) - J_X^\star)^2}{(J_X^{max} - J_X^\star)^2}$$

Marler & Arora, Struct. Multidiscipl. Optim.

Macroscopic outputs and data fitting

Specific choice for the division rates and parameter set





$$\gamma_1 + \frac{\gamma_0 - \gamma_1}{1 + e^{s_\gamma (t - t_\gamma)}}$$

$$\frac{K_{AP}\, e^{s_+(t-t_+)}}{(1 + e^{s_+(t-t_+)})(1 + e^{s_-(t-t_-)})}$$

Estimated parameters

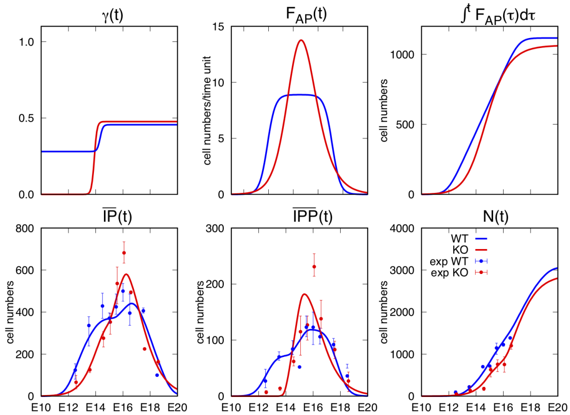
$$\theta = \{K_{AP}, s_+, t_+, s_-, t_-, \gamma_0, \gamma_1, s_\gamma, t_\gamma\}$$

Fixed parameters

Cell cycle duration and durations of cell cycle phases G1, S, G2, M *(Arai et al. Nat. Commun. 2011)*

Macroscopic outputs and data fitting

Optimization results in the control and mutant cases



Negligible direct neurogenesis rate
Time-varying $\gamma(\mathbf{t})$ (ratio of IPP/IPN born by AP divisions)
Comparable neuronal output and cumulated AP inflow, yet **different timing**
Shorter duration of neurogenesis in KO
Plateau-shaped (CTL) versus **peak-shaped** (KO) change in instantaneous AP inflow

Stochastic model

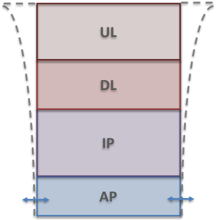
Beyond deterministic modeling outputs

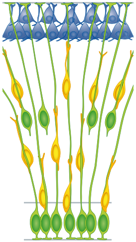
Main results

- Nested compartmental and age-structured model
- Focus on IP cell dynamics
  - Pivotal cell type
  - Cell kinetics viewpoint
- Functional hypotheses for Ftm -/- mutants
- A multiscale mathematical model of cell dynamics during neurogenesis in the mouse cerebral cortex https://doi.org/10.1186/s12859-019-3018-8
- Simulation environment (Python Notebook) https://github.com/letsop/cemone

Motivations for a stochastic approach

- Intrinsic stochasticity in cell decision making
- vs Extrinsic stochasticity
  - Experimental sampling (in space and time)
  - Neuronal "leakage"
- Distribution of cell cycle/phase duration
- Inside-first outside-last neuron layering





Fernández et al. EMBO J 2016

Beyond deterministic modeling outputs

Bases of the stochastic model

- Probabilistic cell decision making (*time-varying probabilities*)
- (Possibly) stochastic cell cycle duration
- Neuron allocation to deeper/upper layers

Formalism of Compound Poisson Processes

$X(t)$ is a CPP if it can be represented by $X(t) = \sum_{i=1}^{N(t)} Y_i$

$N(t)$ is a Poisson process

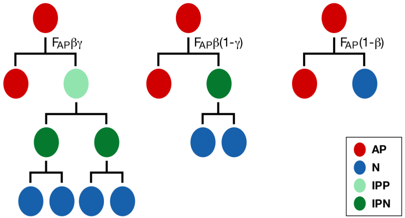
Number of AP-derived cells committed to one or another neurogenic pathway

$(Y_i)_{1 \leq i \leq N_t}$ are random variables independent conditionally to the sequence of arrival times $(T_k)_{k \in \mathbb{N}}$

Choice of the neurogenic pathway

Stochastic framework : Non-homogenous Compound Poisson processes

Arrival times and event choice



event 1 $\quad AP \longrightarrow AP + IPP \xrightarrow{T_{IPP}} 2IPN \xrightarrow{T_{IPN}} \mathbf{4N}$

event 2 $\quad AP \longrightarrow AP + IPN \xrightarrow{T_{IPN}} \mathbf{2N}$

event 3 $\quad AP \longrightarrow AP + \mathbf{N}$

1. Asymmetric divisions of AP

   $Z_t^{AP} = \sum_{k \geq 1} 1_{\{T_k \leq t\}}$: Poisson point process with intensity $F_{AP}(t)$

2. Neural output : "choice" of daughter cell type

   Given arrival times T_k : $Y_k = i \iff$ event i occurred at T_k

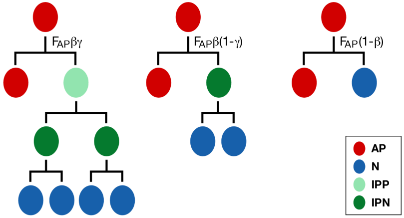
$$\mathbb{P}[Y_k = i | T_k] = \begin{cases} \gamma(T_k)\beta(T_k) \text{ if } i = 1 \\ (1 - \gamma(T_k))\beta(T_k) \text{ if } i = 2 \\ 1 - \beta(T_k) \text{ if } i = 3 \end{cases}$$

Number of events i

$$Z_t^{(i)} = \sum_{k=1}^{Z^{AP}(t)} \mathbb{1}_{Y_k = i}$$

Stochastic framework : Non-homogenous Compound Poisson processes

Delay before neuron production



event 1	$AP \longrightarrow AP + IPP \xrightarrow{T_{IPP}} 2IPN \xrightarrow{T_{IPN}} \mathbf{4N}$
event 2	$AP \longrightarrow AP + IPN \xrightarrow{T_{IPN}} \mathbf{2N}$
event 3	$AP \longrightarrow AP + \mathbf{N}$

- Delay between the commitment event and neuron production
  marked Poisson point process
- Deterministic cell cycle duration $T_{IPP} \neq T_{IPN}$
- Stochastic duration $\Rightarrow$ additional stochastic variables
  S_k (IPP) $R_k^{(1,i)_{i\in 1,2}}$ (IPN, event 1) R_k^2 (IPN, event 2)
- Exponential, Gamma or Beta(-symmetric) law
  explicit control of variance and expectation from the parameter values

Assessing cell numbers at $T_k \leq t \leq T_{k+1}$

- Number of past events
- Time elapsed since latest events 1 and 2

  Is the IPP generated by latest event 1 still alive?

  Are the IPNs arisen from latest events 1 and 2 still alive?

$$IPP(t) = \sum_{k=1}^{\overbrace{Z_t^{AP}}^{AP\ div}} \underbrace{\mathbb{1}_{Y_k=1}}_{event\ type} \underbrace{\mathbb{1}_{t<T_k+T_{IPP}}}_{cell\ cycle},$$

$$IPN(t) = \sum_{k=1}^{Z_t^{AP}} \left(2.\mathbb{1}_{Y_k=1}\mathbb{1}_{T_k+T_{IPP}\leq t<T_k+T_{IPP}+T_{IPN}} + \mathbb{1}_{Y_k=1}\mathbb{1}_{t<T_k+T_{IPN}}\right),$$

$$N(t) = \sum_{k=1}^{Z_t^{AP}} \left(4.\mathbb{1}_{Y_k=1}\mathbb{1}_{T_k+T_{IPP}+T_{IPN}\leq t} + 2.\mathbb{1}_{Y_k=2}\mathbb{1}_{T_k+T_{IPN}\leq t} + \mathbb{1}_{Y_k=3}\right).$$

Stochastic framework : Non-homogenous Compound Poisson processes

From event numbers to cell numbers

Assessing cell numbers at $T_k \leq t \leq T_{k+1}$

- Number of past events
- Time elapsed since latest events 1 and 2

  Is the IPP generated by latest event 1 still alive?

  Are the IPNs arisen from latest events 1 and 2 still alive?

Stochastic cell cycle duration

- discriminate IPN daughter cells engendered by a same event 1
  two asynchronous pairs of neurons
- discriminate IPN cells engendered by either event 1 or 2

Theorem

(Direct adaptation of Chen & Savits Statist. Probab. Lett. 1993)
Let $(X_t)_{t\geq 0}$ *a* $\mathbb{R}$*-valued, non-homogenous Poisson Process, with intensity* $\lambda : \mathbb{R}^+ \longrightarrow \mathbb{R}^+$ *and stochastic kernels* $(L_t)_{t\geq 0}$*. Then for* $t \geq 0$*:*

$$\mathbb{E}[X_t] = \int_0^t \int_{\mathbb{R}} y L_t(s, dy)\lambda(s)ds,$$

$$Var(X_t) = \int_0^t \int_{\mathbb{R}} y^2 L_t(s, dy)\lambda(s)ds.$$

Instance for IPP(t) (deterministic cell cycle duration)

1. Apply to the counting process of each event $Z_t^{(i)}$

$$\mathbb{E}[Z_t^{(1)}] = \int_0^t \gamma(s)\beta(s)F_{AP}(s)ds$$

2. Express cell numbers from the proper combination of $Z_t^{(i)}$
   remove all cells that have completed a full cycle

$$IPP(t) = \sum_{k=1}^{Z_t^{AP}} \mathbb{1}_{Y_k=1, t-T_k<T_{IPP}} = Z_t^{(1)} - Z_{t-T_{IPP}}^{(1)} \mathbb{1}_{t \geq T_{IPP}}$$

3. Compute the expectation and variance
   trace back to the delay elapsed since cell cycle has begun

$$\mathbb{E}[IPP(t)] = \int_{\max(t-T_{IPP},0)}^t \gamma(s)\beta(s)F_{AP}(s)ds$$

"Extrande" variant of Gillespie algorithm (Voliotis *et al.*, *PloS Comp. Biol.* 2016)

$F_{AP}(t)$ bounded : For all $t \geq 0$ $F_{AP}(t) \leq \bar{F}$

Introduce $(R_t)_{t\geq 0}$ Poisson process with intensity $\bar{F} - F_{AP}(t)$

New simulated process $\overline{Z_t} = (Z_t, R_t)$
Events occur at rate $F_{AP}(t) + \bar{F} - F_{AP}(t) = \bar{F}$

$Z_t = (IPP(t), IPN(t), N(t))$ given by the first coordinates of $\overline{Z_t}$

1. Simulate the next update time $(t + t_{event})$ from an Exponential law;
2. Select the division type (event 1, 2 or 3), through classical acceptance-reject from the realization of a stochastic variable following a Uniform distribution;
3. In the case of stochastic cell cycle durations, compute the value of T_{IPP} and/or T_{IPN} through the inverse of the distribution functions G_{IPP}^{-1} and/or G_{IPN}^{-1} applied to the realization a Uniform distribution;
4. Update the cell numbers of each cell type (IPP, IPN, N, DL, UL).

Sketch of the pseudocode

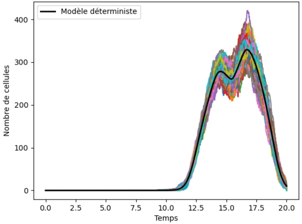
while $t < t_{\text{end}}$ **do**
    $t_{\text{event}} \leftarrow \mathcal{E}(\overline{F})$
    if $t + t_{\text{event}} > t_{\text{end}}$ **then**
        $\text{t} \leftarrow t_{\text{end}}$
    else
        $t \leftarrow t + t_{\text{event}}$
        $\text{whichdiv} \leftarrow U([0,1])\overline{F}$
        if $\text{whichdiv} \leq \gamma(t)\beta(t)F_{AP}(t)$ **then**
            $T_{IPP} = G_{IPP}^{-1}(U([0,1]))$ $\text{IPP}[t : t + T_{IPP}] \mathrel{+}= 1$
            for $i = 1, 2$ **do**
                $T_{IPN}^{(i)} = G_{IPN}^{-1}(U([0,1]))$ $\text{IPN}[t + T_{IPP} : t + T_{IPP} + T_{IPN}^{(i)}] \mathrel{+}= 1$
        else if $\gamma(t)\beta(t)F_{AP}(t) \leq \text{whichdiv} \leq \beta(t)F_{AP}(t)$ **then**
            $T_{IPN} = G_{IPN}^{-1}(U([0,1]))$
            $\text{IPN}[t : t + T_{IPN}] \mathrel{+}= 1$ $\text{N}[t + T_{IPN} : \text{end}] \mathrel{+}= 2$
        else if $\beta(t)F_{AP}(t) \leq \text{whichdiv} \leq F_{AP}(t)$ **then**
            $\text{N}[t : \text{end}] \mathrel{+}= 1$
        else
            Nothing (update R_t)
return times, IPP, IPN, N

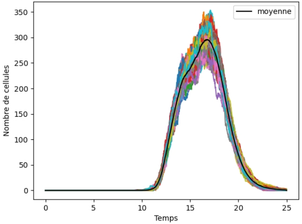
Theoretical and numerical results

Stochastic/deterministic simulations / Instance of the IPN dynamics

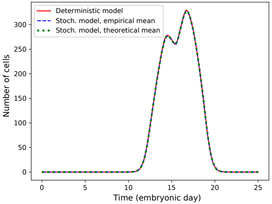
Fixed cycle duration **Stochastic cycle duration**

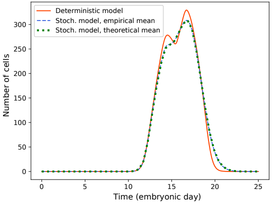
Trajectories vs deterministic model





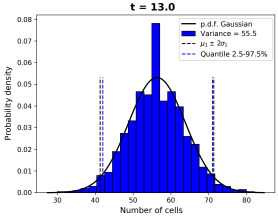
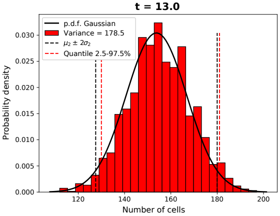
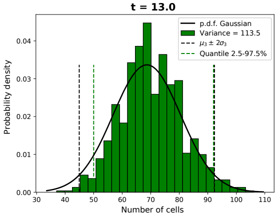
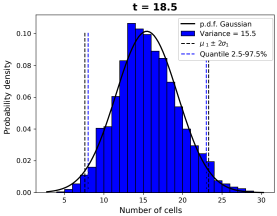
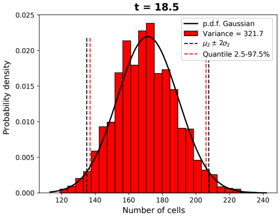
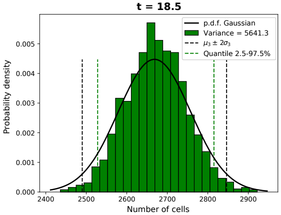
Expectation, empirical mean and deterministic model





Cell number variance

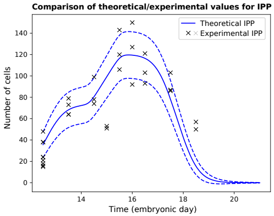
Empirical distribution and 95% quantiles

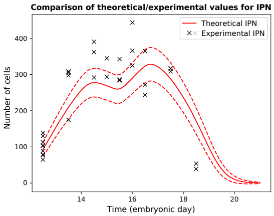
	IPP(t)	IPN(t)	N(t)
E13.5			
E18.5			

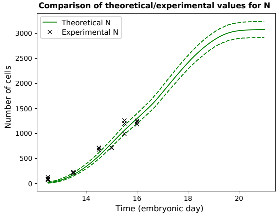
Theoretical and numerical results

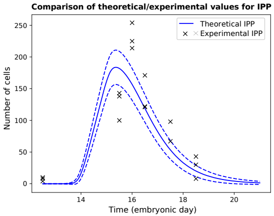
Data fitting

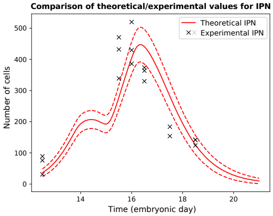
IPP(t) | **IPN(t)** | **N(t)**

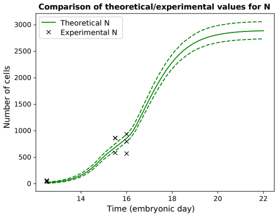












- $\mathrm{Var}(N_T)$ increases with N_T (and T)
  $\Rightarrow$ analysis at fixed (biologically-realistic) expected final $\mathbb{E}(N_T)$
- 3 components corresponding to the 3 pathways I_1, I_2, I_3
  $\Rightarrow$ trick to study their relative weight in 2D, given that $4I_1 + 2I_2 + I_3 = \mathbb{E}(N_T)$

$$\mathrm{Var}(N_t) = 16\left(\underbrace{\int_0^{t-T_{IPP}-T_{IPN}} \gamma(s)\beta(s)F_{AP}(s)ds}_{I_1}\right)\mathbb{1}_{t\geq T_{IPP}+T_{IPN}}$$

$$+\,4\left(\underbrace{\int_0^{t-T_{IPN}} (1-\gamma(s))\,\beta(s)F_{AP}(s)ds}_{I_2}\right)\mathbb{1}_{t\geq T_{IPN}}$$

$$+\underbrace{\int_0^{t} (1-\beta(s))\,F_{AP}(s)ds}_{I_3}$$

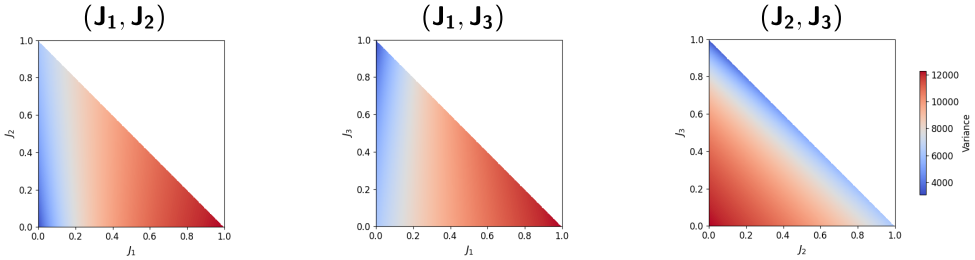
$$J_1 = I_1/(I_1+I_2+I_3),$$
$$J_2 = I_2/(I_1+I_2+I_3),$$
$$J_3 = I_3/(I_1+I_2+I_3)$$

$$f(x,y,z) = 16x + 4y + z$$
$$f(I_1,I_2,I_3) = \mathrm{Var}(N_T)$$

$$\mathrm{Var}(N_T) = \begin{cases} h_1(J_1,J_2) \\ h_2(J_1,J_3) \\ h_3(J_2,J_3) \end{cases}$$

Impact of the neurogenic pathway

Variance of the final neuron number

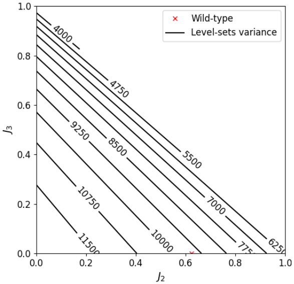


- **Minimal variance** with only event 3 ($J_3 = 1$, direct neurogenesis)
  not consistent with the length of the neurogenic window and/or the division rate of AP
- **Maximal variance** with only event 1 ($J_1 = 1$, IPP pathway)
  not consistent with the first arrival times of neurons

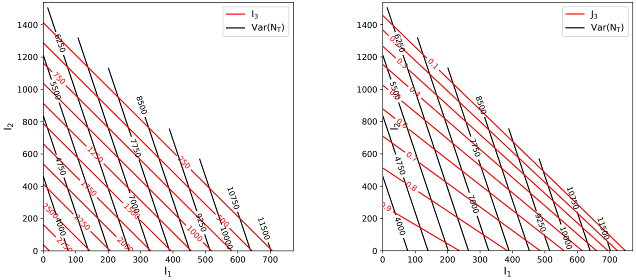
Impact of the neurogenic pathway

Variance of the final neuron number

$(\mathbf{J_2}, \mathbf{J_3})$

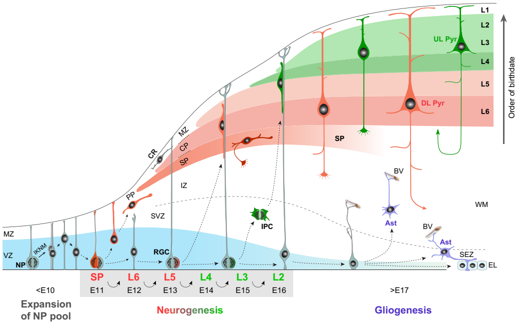


$(\mathbf{I_1}, \mathbf{I_2})$



- **Subtle effects in mixed regimen** *according to the concomitant changes in* J_1 *and* J_2
  $\delta I_2 = -6\delta I_1 \Rightarrow$ constant $\mathrm{Var}(N_T)$
  $\delta I_2 > -6\delta I_1 \Rightarrow$ increase in $\mathrm{Var}(N_T)$
  $\delta I_2 < -6\delta I_1 \Rightarrow$ decrease in $\mathrm{Var}(N_T)$

Neural layering: upper/lower layer repartition



Kwan et al. Development 2012

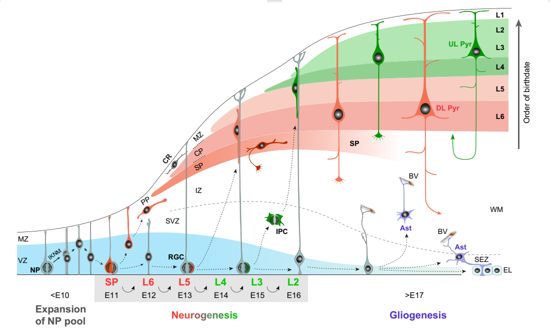
Inside-first outside-last neuron layering with stochasticity

$\Rightarrow$ probability dependent on neuron birth date

$$\Delta(t) = \mathbb{P}[N_i \in DL | \text{birth} = t]$$

$$= \Delta_1 + \frac{\Delta_0 - \Delta_1}{\left(1 + e^{s_\Delta (t - t_\Delta)}\right)}$$

Neural layering: upper/lower layer repartition



Kwan et al. Development 2012

Inside-first outside-last neuron layering with stochasticity

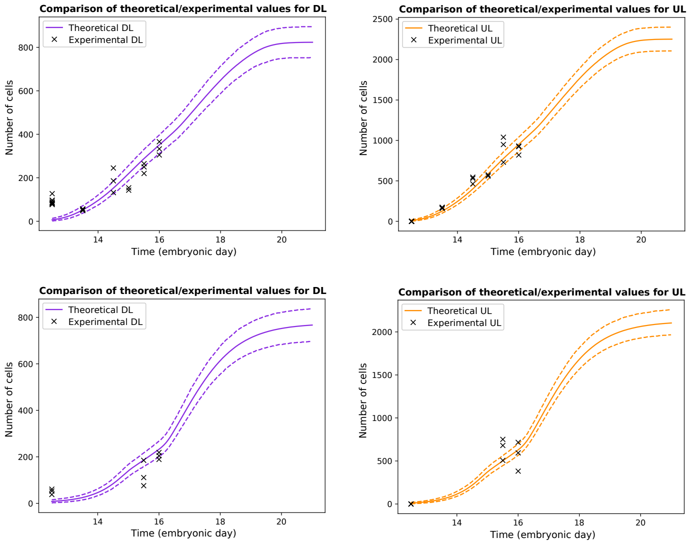
$\Rightarrow$ probability dependent on neuron birth date

$$\Delta(t) = \mathbb{P}[N_i \in DL | \text{birth} = t]$$
$$= \Delta_1 + \frac{\Delta_0 - \Delta_1}{\left(1 + e^{s_\Delta (t - t_\Delta)}\right)}$$

$$DL(t) = \sum_{k=1}^{Z_t^{AP}} \left(\mathbb{1}_{Y_k=1} \mathbb{1}_{T_k + T_{IPP} + T_{IPN} \leq t} B_k^{(1)} + 1_{Y_k=2} \mathbb{1}_{T_k + T_{IPN} \leq t} B_k^{(2)} + \mathbb{1}_{Y_k=3} B_k^{(3)} \right)$$

$$B_k^{(1)} | T_k = \text{Binom}(4, \Delta(T_k + T_{IPP} + T_{IPN})),$$
$$B_k^{(2)} | T_k = \text{Binom}(2, \Delta(T_k + T_{IPN})),$$
$$B_k^{(3)} | T_k = \text{Binom}(1, \Delta(T_k)).$$

Neural layering: upper/lower layer repartition

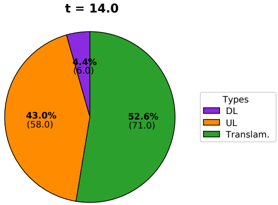


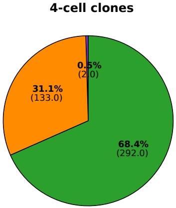
Neural layering: upper/lower layer repartition

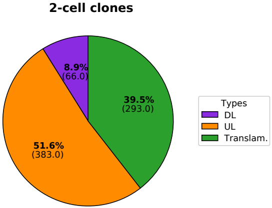
Clonal viewpoint

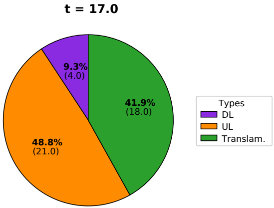
Translaminar clones

- 2- or 4-cell clones engendered by each AP division
- Look at the location of neurons derived from the same ancestor cell according to arrival time or clone size
- ⇒ deeper, upper and translaminar clones







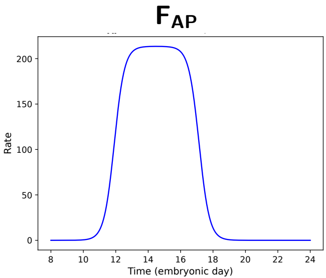


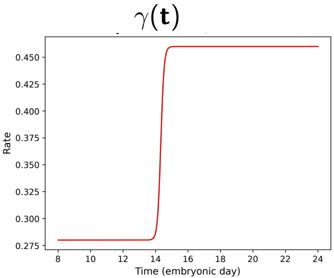
Possible extensions

1. State-varying rates
2. Explicit AP dynamics
3. Enriched IP dynamics
4. Analysis of lineage trees

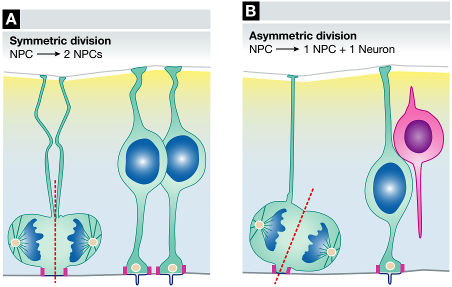
State-varying rates

Time varying rates $\Rightarrow$ feedback functions of state variables ($N(t)$?)

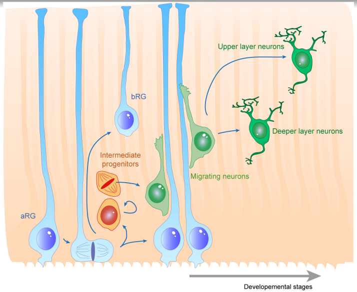




Explicit AP dynamics



Paridaen & Huttner EMBO Rep 2014



Ferrent et al. Front Cell Dev Biol 2020

Motivations

1. Complete the model during the neurogenic period
2. Use available AP numbers despite observation bias
   available numbers are lower bounds
3. Extend the model before neurogenesis starts
   building of the AP pool supporting F_{AP} outflow
4. Pave the way to lineage tracing analysis

Explicit AP dynamics

Simplified AP dynamics piecewise-linear, possibly discrete time (generation number)

If $t < t_{S1}$

$$\begin{cases} AP \xrightarrow{\lambda} AP + AP \\ AP \xrightarrow{\mu} \emptyset \end{cases}$$

If $t_{S1} \leq t < t_{S2}$

$$\begin{cases} AP \xrightarrow{\lambda_{\mathrm{AP}}^{S_1}} AP + AP \\ AP \xrightarrow{\lambda_{\mathrm{IPP}}^{S_1}} AP + IPP \\ AP \xrightarrow{\lambda_{\mathrm{IPN}}^{S_1}} AP + IPN \\ AP \xrightarrow{\lambda_{\mathrm{N}}^{S_1}} AP + N \\ AP \xrightarrow{\mu^{S_1}} \emptyset \end{cases}$$

If $t_{S2} \leq t < t_E$

$$\begin{cases} AP \xrightarrow{\lambda_{\mathrm{AP}}^{S_2}} AP + AP \\ AP \xrightarrow{\lambda_{\mathrm{IPP}}^{S_2}} AP + IPP \\ AP \xrightarrow{\lambda_{\mathrm{IPN}}^{S_2}} AP + IPN \\ AP \xrightarrow{\lambda_{\mathrm{N}}^{S_2}} AP + N \\ AP \xrightarrow{\mu^{S_2}} \emptyset \end{cases}$$

If $t \geq t_E$

$$\begin{cases} AP \xrightarrow{\mu_E} \emptyset \end{cases}$$

$$\forall t \begin{cases} IPP \xrightarrow{T_{IPP}} IPN + IPN \\ IPN \xrightarrow{T_{IPN}} N + N \end{cases}$$

Self-amplification

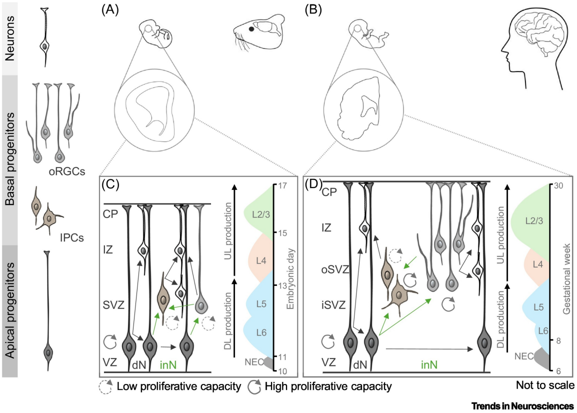
DL neurogenesis

UL neurogenesis

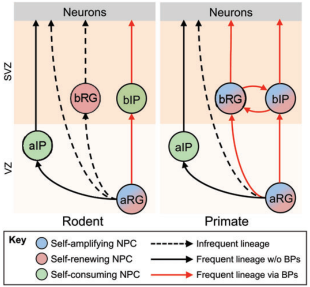
Gliogenesis

Diversified intermediate progenitors

From lissencephalic to gyrencephalic species



Barão & Müller, Trends Neurosci. 2026

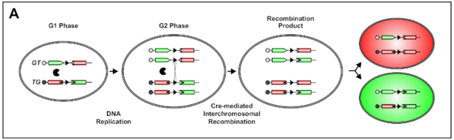


Fliro & Huttner Development 2014

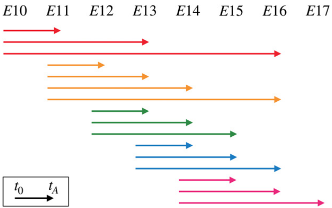
Possible first step: stochastic IPP cycle rounds

Towards a model-based clonal analysis of lineage tracing

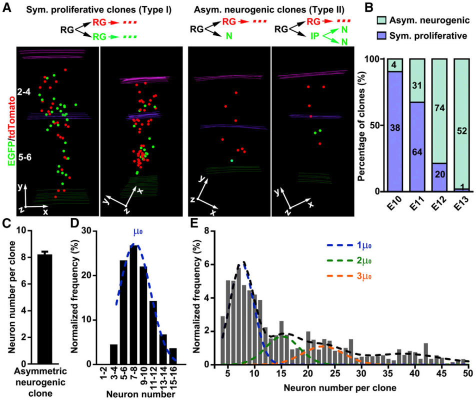
Mosaic Analysis with Double Markers (MADM)



Gao et al., J Vis Exp 2020



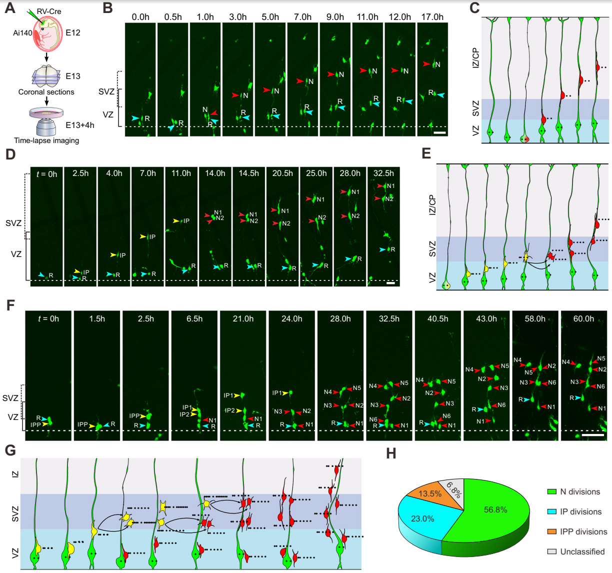
Picco et al., J. Anat. 2020



Gao et al., Cell 2014

Towards a model-based clonal analysis of lineage tracing

Dynamic lineage time-lapse study, *Shen et al., EMBO J 2026*



Towards a model-based clonal analysis of lineage tracing

Inferring the division type probability?

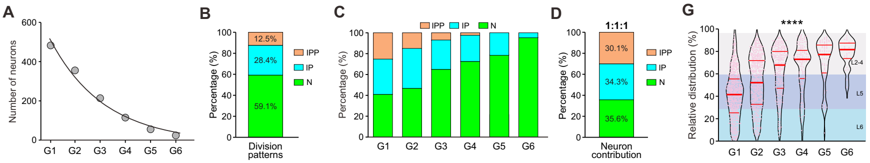
Forward problem : describe the tree and associated outputs

- Distribution of the progenitor (AP) extinction generation number
- Computation of cell numbers of each type at each generation and final neuron number

Backward problem : What can we infer from total or partial observation of the lineage tree?

leaves, nodes, roots / tree topology (symmetry)

- Switch from proliferative to neurogenic division mode of AP
- Contribution of the neurogenic pathways to the final neuron output



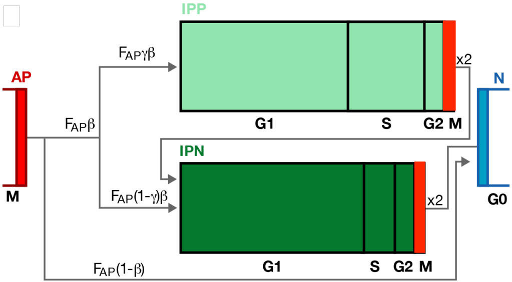
Shen et al., EMBO J 2026

Appendix : More on cell kinetics

Mesoscopic scale : cell kinetics indexes

Mitotic index

Integration in age over phase M – neurogenic fraction (Proportion of neurogenic IP mitoses)



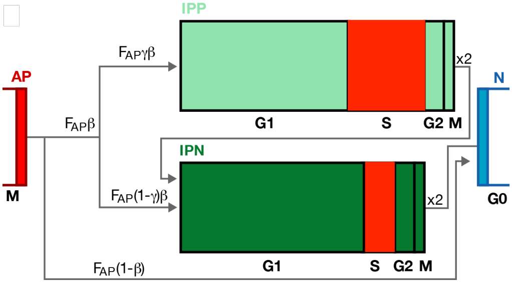
$$\begin{cases} \overline{IPP}_M(t) = \int_{T_c^{IPP}-T_M{IPP}}^{T_c^{IPP}} IPP(t,a)da \\ \overline{IPN}_M(t) = \int_{T_c^{IPN}-T_M{IPN}}^{T_c^{IPN}} IPN(t,a)da \end{cases}$$

$$\begin{cases} MI(t) = \dfrac{\overline{IPP}_M(t) + \overline{IPN}_M(t)}{\overline{IP}(t)} \\ \psi(t) = \dfrac{\overline{IPN}_M(t)}{\overline{IPP}_M(t) + \overline{IPN}_M(t)} \end{cases}$$

Mesoscopic scale : cell kinetics indexes

Labeling index

Integration in age over phase S



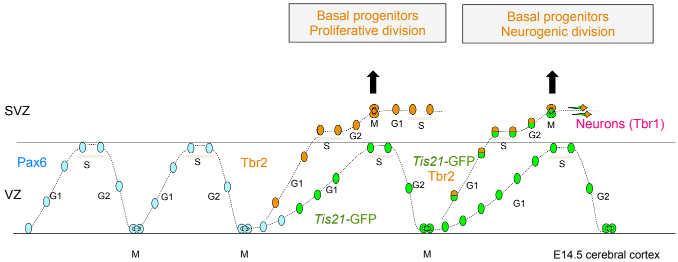
$$\begin{cases} \overline{IPP}_S(t) = \int_{T_{G1}^{IPP}}^{T_{G1}^{IPP}+T_S^{IPP}} IPP(t,a)da \\ \overline{IPN}_S(t) = \int_{T_{G1}^{IPN}}^{T_{G1}^{IPN}+T_S^{IPN}} IPN(t,a)da \end{cases} \qquad LI(t) = \frac{\overline{IPP}_S(t) + \overline{IPN}_S(t)}{\overline{IP}(t)}$$

In silico cell kinetics experiments

Neurogenic fraction

Experimental discrimination between IPgenic and neurogenic IP

Transgenic Tis21 lines

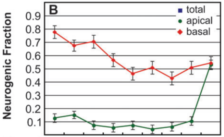


Courtesy Y. Arai

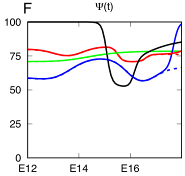
Computation of the neurogenic fraction

$$\psi(t) = \frac{\overline{IPN}_M(t)}{\overline{IPP}_M(t) + \overline{IPN}_M(t)}$$

Proportion of neurogenic IP mitoses



Kowalczyk et al. Cereb. Cortex 2009

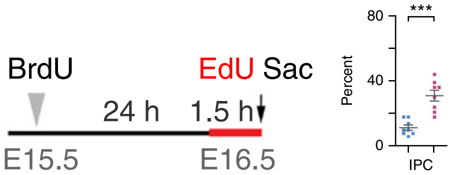


ψ computed from estimated parameters

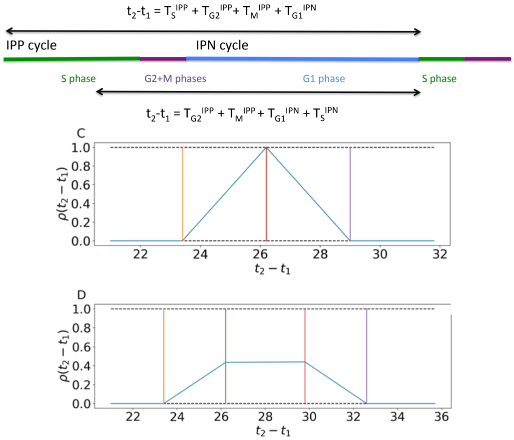
In silico cell kinetics experiments

Long-term double-labeling experiments

Experimental assessment of “IP self-renewal” : tracking IP cells along S phases



Wang et al. Nature Neurosci. 2014



Model-assisted experimentation

Reliability of the tracking subject to

- *the experimental delay* $t_2 - t_1$
- *differences in successive S phase durations*

Computation of the fraction of “recovered” cells $\rho(\mathbf{t2} - \mathbf{t}_1)$

Retrotracing from the characteristic curve solutions

$$
\begin{cases}
IPP(t,0) & = & \gamma(t)\beta(t)F_{AP}(t) \\
IPP(t,a) & = & \begin{cases} IPP(0,a-t) \text{ for } t < a < T_C^{IPP} \\ IPP(t-a,0) \text{ for } 0 < a < t \end{cases} \\
IPN(t,0) & = & (1-\gamma(t))\beta(t)F_{AP}(t) + 2IPP(t, T_C^{IPP}) \\
IPN(t,a) & = & \begin{cases} IPN(0,a-t) \text{ for } t < a < T_C^{IPN} \\ IPN(t-a,0) \text{ for } 0 < a < t \end{cases}
\end{cases}
$$