Parameter Estimation and Mechanistic Modeling of Adult Zebrafish Neurogenesis

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May 2025

Section 1

Zebrafish Neurogenesis

What is Neurogenesis

- **ADULT NEUROGENESIS:** Generation of mature neurons from neural stem cells (NSCs) in adult brains. (*i.e.: after sexual maturity is reached*)

- **REGION OF INTEREST:** Dorso-medial (Dm) area of Pallium, in the telencephalon.

- **NSC PROGRESSION:** Quiescent $\leftrightarrow$ Active $\rightarrow$ NP $\rightarrow$ neurons

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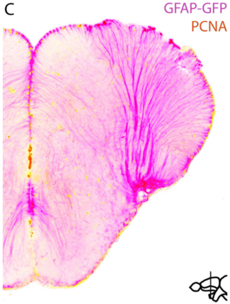

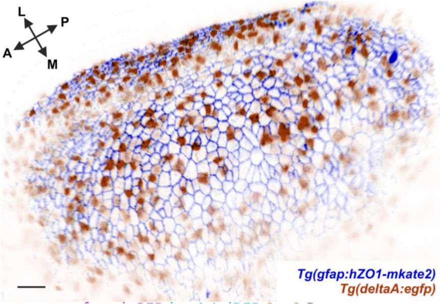

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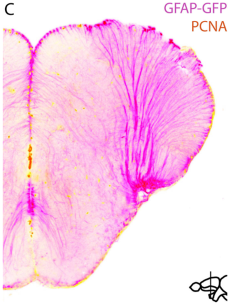

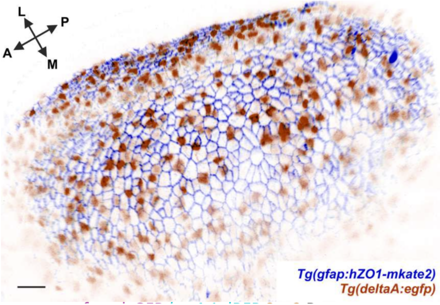

- **NSC progression:** Quiescent ↔ Active → NP → neurons

Mathematical Modeling of NSC Dynamics

- Dynamical homeostasis.
- Targeted interventions could counteract NSC ageing effects.
- Mechanistic models help interpret complex lineage behavior when experiments are limited.
- Previous models for mouse used linear ODEs with time-dependent parameters:

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Results

- New model harboring feedback integration (blue and red function):

$$\begin{cases} \dfrac{d(qNSC)}{dt}(t) =: u'(t) = -a(t)u(t) + 2b(t)v(t), \\ \dfrac{d(aNSC)}{dt}(t) =: v'(t) = a(t)u(t) - v(t), \\ \dfrac{d(NP)}{dt}(t) =: w'(t) = 2\left(1 - b(t)\right) v(t) - \delta w(t), \end{cases}$$

State variables:

- $u(t) \geq 0$: number of qNSC.
- $v(t) \geq 0$: number of aNSC.
- $w(t) \geq 0$: number of NP.

Parameters:

- $a_0, K > 0$: activation rate regulation.
- $b_0, \beta > 0$: self-renewal rate regulation.
- $\delta > 0$: death / migration rate of NPs.

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Feedback functions

(no feedback): Constant feedback (*equivalent to averaging feedback in space*), bad fitting.

$$(M_0) \qquad a = a_0 \qquad b(u,v,w) = b_0$$

(feedback): Hill-type feedback of the form Const. $\times \frac{\text{Activator}}{\text{Const.} + \text{Inhibitor}}$

$$(M_1) \qquad a(u,v) = a_0 \frac{u}{K+v}, \qquad b(v) = b_0 \frac{1}{1+\beta v}$$

$$(M_2) \qquad a(u,v) = a_0 \frac{u}{K+v}, \qquad b(u) = b_0 \frac{1}{1+\beta u}$$

$$(M_3) \qquad a(u,v) = a_0 \frac{u}{K+v}, \qquad b(w) = b_0 \frac{1}{1+\beta w}$$

$$(M_4) \qquad a(u+v,u+v) = a_0 \frac{u+v}{K+(u+v)}, \qquad b(u+v) = b_0 \frac{1}{1+\beta(u+v)}$$

$$(M_5) \qquad a(u,w) = a_0 \frac{u}{K+w}, \qquad b(w) = b_0 \frac{1}{1+\beta w}$$

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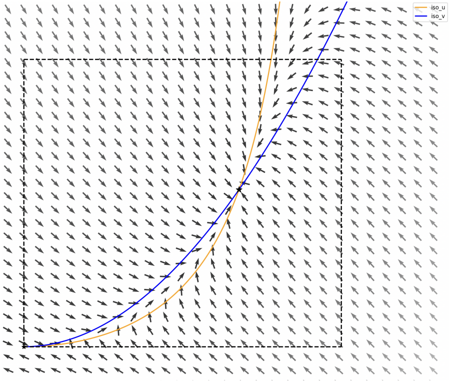
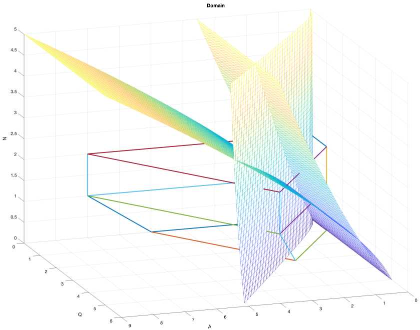
Well-posedness of the problem ($b_0 > 1/2$)[1]

- Finite cell numbers for all times (global existence of a solution $\forall T \geq 0$).
- Non extinction of population ($\exists$ steady state $\boldsymbol{X}^\star > 0$ s.t. $\boldsymbol{X}(t) \xrightarrow{t \nearrow +\infty} \boldsymbol{X}^\star$).



for $(M_1), (M_2), (M_4)$.



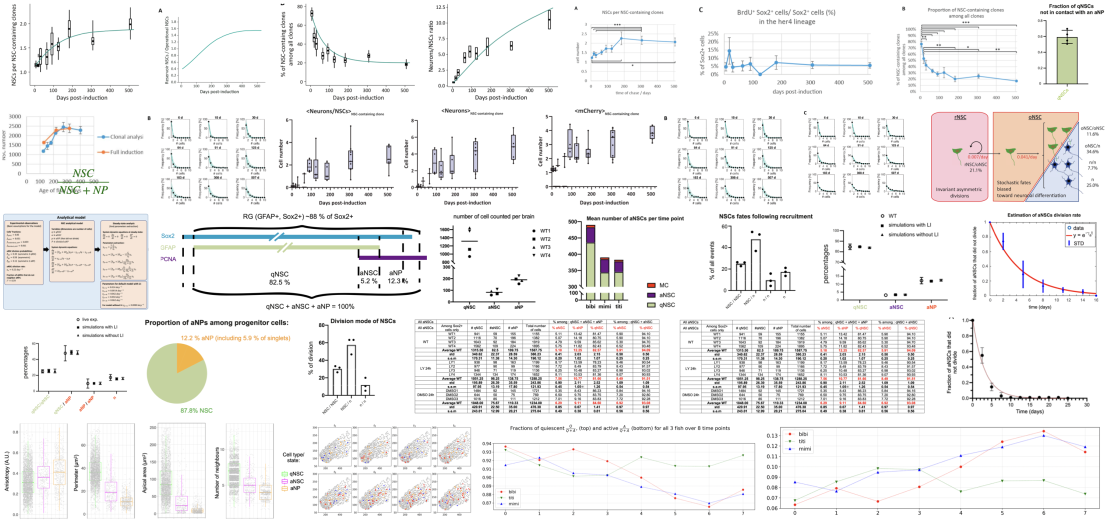
for $(M_3), (M_5)$.

[1]when $b_0 \leq 1/2$, we have $\frac{d(u+v)}{dt} \leq 0$ so $\boldsymbol{X}(t) \to \mathbf{0}$, whenever $t \to +\infty$.

But how good is this model?

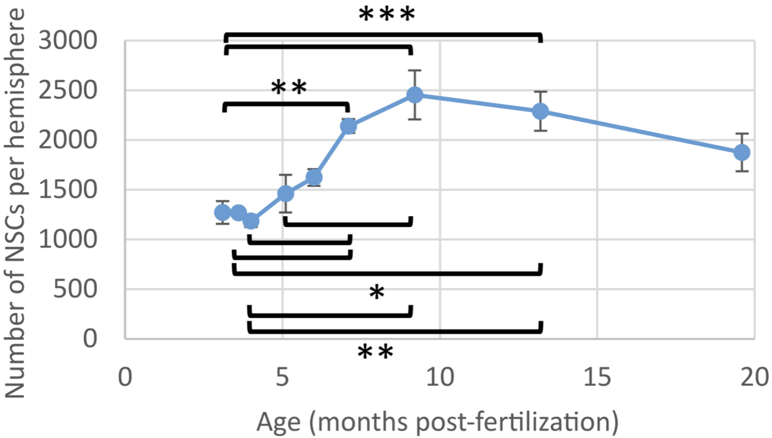
Biological data

$\hookrightarrow$ A lot of available data... but very few is actually **usable**. ☹



Biological data

- ↪ A lot of available data... but very few is actually **usable**. ☹
- ↪ Time series (t_i, y_i) of total NSC + NP population (identified by `Sox2+` fluorescence).



Goal: fit model to this dataset.

Calibration pipeline (for each feedback $a(c_1, c_2)$, $b(c_3)$)

1. Let $\vartheta \in \boldsymbol{\Theta} \subset \mathbb{R}^6$. Denote by $\boldsymbol{x}_\vartheta := \left(u_\vartheta, v_\vartheta, w_\vartheta\right)^T \in \mathbb{R}^3_{\geq 0}$, the solution to the IVP

$$\frac{d\boldsymbol{x}_\vartheta}{dt}(t) = \boldsymbol{F}\left(\boldsymbol{x}_\vartheta(t),\, \vartheta\right) := \begin{pmatrix} \boldsymbol{F}_1(\boldsymbol{x}_\vartheta,\, \vartheta) \\ \boldsymbol{F}_2(\boldsymbol{x}_\vartheta,\, \vartheta) \\ \boldsymbol{F}_3(\boldsymbol{x}_\vartheta,\, \vartheta) \end{pmatrix} \qquad \text{(model equations)}$$

$$\boldsymbol{x}_\vartheta(0) = \boldsymbol{x}_0(\vartheta) \in \mathbb{R}^3_{\geq 0} \qquad \text{(initial value)}$$

2. Introduce the data set: $\left\{(t_i, y_i^{\text{obs}})\right\}_{i=1}^{N_{\text{obs}}}$ (*total number of NSC + NP in the system w.r.t. age*)
3. Solve the minimization problem:

$$\text{find } \hat{\vartheta} \text{ s.t.} \qquad \hat{\vartheta} := \text{argmin}_{\theta\in\Theta} \sum_{i=1}^{N_{obs}} \left\| \underbrace{y_i^{\text{obs}} - \sum_{j=1,2,3} \left(\boldsymbol{x}_{0,j}(\vartheta) + \int_0^{t_i} \boldsymbol{F}_j(\xi, \vartheta) d\xi \right)}_{\text{distance sum of all cells to observation}} \right\|^2$$

4. If method converges: the best parameter is $\vartheta = \hat{\vartheta}$.

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Fitted curves

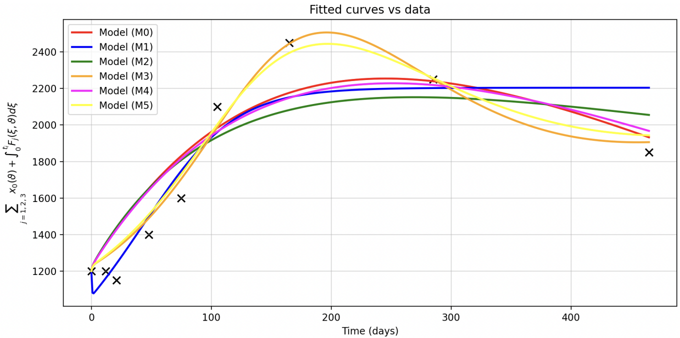
- Best fit: feedback M_3

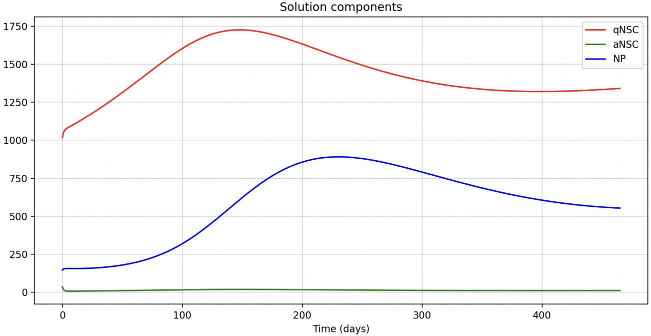
$\hookrightarrow$ $a(u, v)$ and $b(w)$

$\hookrightarrow$ regulation by both aNSC and NP.

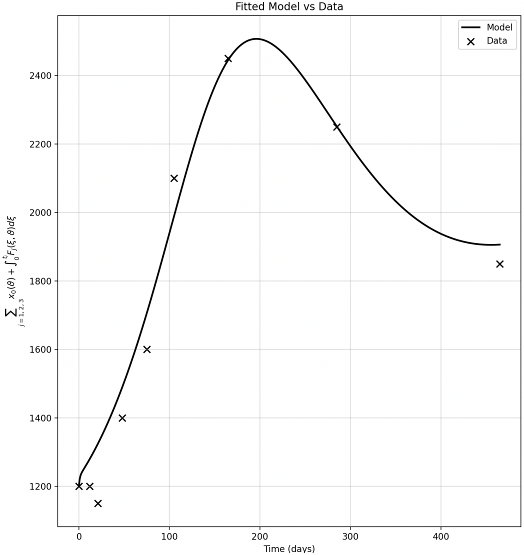
- The covariance matrix $\Sigma(\vartheta)$ has a "small" condition number $(\lambda_1 \times \lambda_N)$.

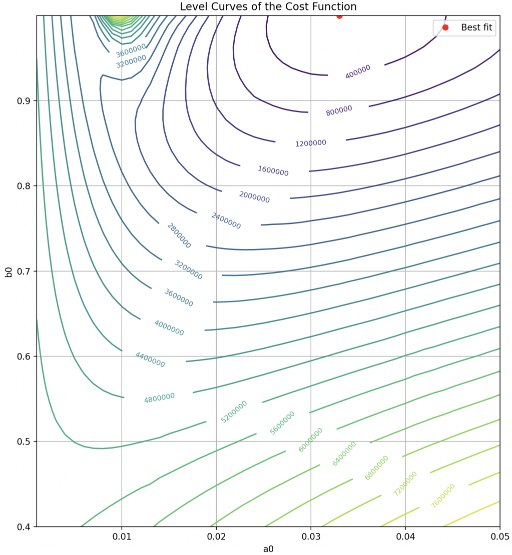
$\hookrightarrow$ No overfitting.





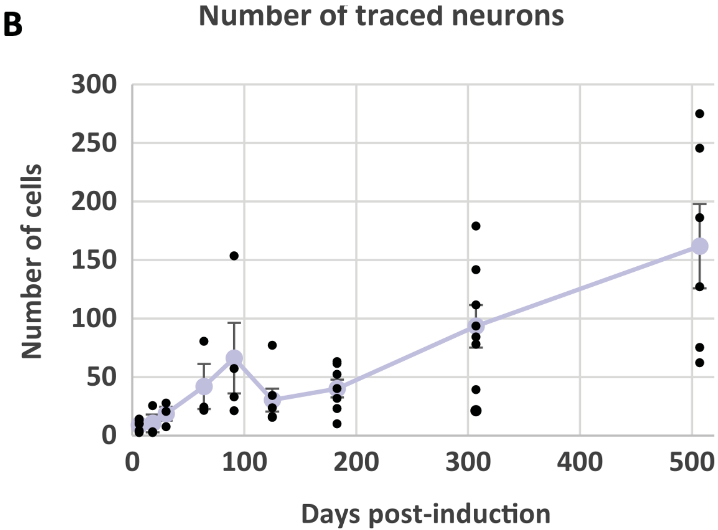
Calibrated best feedback and associated loss function





New data?

Goal: Manually cure and integrate the following dataset.[2]



[2]Experiment $n = 6, 3, 3, 3, 4, 6, 7, 9$, and 7 brains at 6, 18, 30, 64, 91, 125, 183, 307, and 507 dpi resp.

New data?

- Use the new dataset $\left\{\left(\tau_i, z_i^{\text{obs}}\right)\right\}_{i=1}^{M_{\text{obs}}}$ (from the same paper $\implies$ low heterogeneity):

$\hookrightarrow$ Fit to the cumulative number of neurons over time:

$$CN(t) \propto \int_0^t w(\xi) d\xi$$

- Invites an adjusted definition the loss function

$$\tilde{J}(\vartheta) := \frac{1}{\omega_1} \sum_{i=1}^{N_{obs}} \left\| y_i^{\text{obs}} - \sum_{j=1,2,3} \left(\boldsymbol{x}_{0,j}(\vartheta) + \int_0^{t_i} \boldsymbol{F}_j(\xi, \vartheta) d\xi \right) \right\|^2 + \frac{1}{\omega_2} \sum_{i=1}^{M_{obs}} \left\| z_i^{\text{obs}} - \kappa \int_0^{\tau_i} w(\xi) d\xi \right\|^2$$

Section 2

Progress I could not mention here

Three theorems for Hydra project (I)

Theorem (Bistability)

Let $\mu_1, \mu_2, \mu_3 \in (0,1]$, $m_1, m_2, m_3 \in [2, +\infty)$, *and* $\eta_1, \eta_2, \eta_3, \alpha$ *as defined above. Suppose that parameters of the model additionally satisfy the relations*

1. $\zeta > 0$, *where* $\zeta := \alpha - 2\mu_2 > 0$,
2. $\Theta > 0$, *where* $\Theta := \zeta^2 - 4\mu_2(\mu_2 + \eta_3)$,
3. $\alpha + 2\eta_3 + \sqrt{\Theta} > 2(\frac{\mu_1}{\mu_3} - 1)(\mu_2 + \eta_3)\frac{\eta_1\eta_3}{m_1+m_2}$,

Then, the associated kinetic system is bistable, with three nonnegative steady states $\bar{\boldsymbol{X}}_{\boldsymbol{O}} := (0,0,0)^T$, *and* $\bar{\boldsymbol{X}}_{u,s}$, *where*

$$\bar{\boldsymbol{X}}_{u,s} = (\bar{u}_{u,s}, \bar{v}_{u,s}, \bar{w}_{u,s}) = \left(\eta_1 - \frac{1}{\bar{v}_{u,s}},\ \frac{\alpha + 2\eta_3 \pm \sqrt{\Theta}}{2\eta_1(\mu_2 + \eta_3)},\ \eta_3 - \frac{\eta_3}{\eta_1 \bar{v}_{u,s}}\right),$$

where $\bar{\boldsymbol{X}}_u$ *is associated to "$-$", and* $\bar{\boldsymbol{X}}_s$ *to "$+$".*

Three theorems for Hydra project (II)

Theorem (Instability of J_{12})

Let $\mu_1, \mu_2, \mu_3 \in (0, 1]$, $m_1, m_2, m_3 \in [2, +\infty)$, and $\eta_1, \eta_2, \eta_3, \alpha$ as defined above. Moreover, suppose conditions 1., 2., 3. from Theorem 6.1 hold, and that

4.
$$\eta_1 < 2\left(\frac{\eta_3}{m_2} + \frac{2}{\eta_2}\right).$$

Then, the spectral bound $s(J_{12})$ is positive, and there exists either a d_1 small enough, or a couple $d_2 > 0$, $L \geq 1$ both large enough such that $\bar{\boldsymbol{X}}_s$ exhibits DDI.

Three theorems for Hydra project (III)

Theorem (Diffusion thresholds)

On the domain $\Omega = (0, L)$, the positive constant steady state $\bar{\boldsymbol{X}}_s$ exhibits DDI if either of the following conditions holds.

(i) $L > 0$, *the diffusion coefficient* $d_2 > 0$ *is fixed and*

$$0 < d_1 < \frac{\det(J) - \det(J_{12})\, d_2 \lambda_j}{\lambda_j\,(\det(J_{13}) - J_1\, d_2 \lambda_j)}$$

holds for at least one $j \in \mathbb{N}$,

(ii) $d_1 > 0$ *fixed, and*

$$L > \pi j \sqrt{\frac{J_1\, d_1}{\det(J_{12})}}, \qquad d_2 > \frac{\det(J) - \det(J_{13})\, d_1 \lambda_j}{\lambda_j (\det(J_{12}) - J_1\, d_1 \lambda_j)} > 0$$

holds for at least one $j \in \mathbb{N}$.

Sensitivity Equations

4. Sensitivity Analysis

Consider the following ODE system governing NSC dynamics

$$\frac{dy_i}{dt}(t) = f_i(t, \boldsymbol{Y}(t, \boldsymbol{\Theta}) \,|\, \boldsymbol{\Theta}),$$

with the notation $\boldsymbol{Y} = (y_i)_{i=1}^n$, $n = 4$ and the coordinates of $\boldsymbol{Y}$ correspond to state variables Q_R, A_R, Q_O, A_O respectively. The parameters of the model, θ_j, $j = 1, \dots, p$, are gathered in a tuple $\boldsymbol{\Theta} \subset \mathbb{R}^p_{>0}$. They are assumed unknown. We introduce $n \times p$ new variables, noted S_{ij}, which measure the sensitivity of the solution with respect to the parameters $\boldsymbol{\Theta}$

$$S_{ij} = \frac{\partial y_i}{\partial \theta_j}, \quad i = 1, \dots, n, \quad j = 1, \dots, p.$$

These variables satisfy the new differential equation, which we derive by mean of the chain rule and by interchanging the order of derivatives for mixed partials. It holds

$$\frac{\partial S_{ij}}{\partial t} = \frac{\partial}{\partial t}\frac{\partial y_i}{\partial \theta_j} = \frac{\partial}{\partial \theta_j}\frac{\partial y_i}{\partial t},$$

or

$$\frac{\partial S_{ij}}{\partial t} = \frac{\partial}{\partial \theta_j} f_i = \frac{\partial f_i}{\partial \theta_j} + \sum_{k=1}^{n} \frac{\partial f_i}{\partial y_k}\frac{\partial y_k}{\partial \theta_j}.$$

Sensitivity Equations

Let $j \in \{1, \dots, p\}$. Then, for every $i = 1, \dots, n$, the sensitivity variable S_{ij} satisfies the differential equation.

$$\frac{\partial}{\partial t} S_{ij}(t, \boldsymbol{\Theta}) = \frac{\partial f_i}{\partial \theta_j}(t, \boldsymbol{Y}(t, \boldsymbol{\Theta}) \,|\, \boldsymbol{\Theta}) + \sum_{k=1}^{n} \frac{\partial f_i}{\partial y_k} S_{kj}(t, \boldsymbol{\Theta}),$$

The normal sensitivity, $Z_{ij} := S_{ij}\frac{\theta_j}{y_i}$, is then used in order to measure sensitivity in percentages.

Remark: We also phrase the sensitivity equation as a vector differential equation to determine the sensitivity of all variables to one parameter. Let $\boldsymbol{S}_j := (S_{ij})_{i=1}^n$, and recognize the expression of the Jacobi matrix from the original system $\nabla_{\boldsymbol{Y}} \boldsymbol{f} = (\partial_{y_k} f_i)_{1 \le i,k \le n}$. It holds

$$\frac{\partial}{\partial t}\boldsymbol{S}_j(t, \boldsymbol{\Theta}) = \frac{\partial \boldsymbol{f}}{\partial \theta_j}(t, \boldsymbol{Y}(t, \boldsymbol{\Theta}) \,|\, \boldsymbol{\Theta}) + \nabla_{\boldsymbol{Y}} \boldsymbol{f} \cdot \boldsymbol{S}_j(t, \boldsymbol{\Theta})$$

4.1. Sensitivity to self renewal rate: The impact of the self-renewal rate $b \in (0, 1)$, is calculated by solving the associated sensitivity equation

$$\frac{\partial}{\partial t}\boldsymbol{S}(t, b) = \frac{\partial \boldsymbol{f}}{\partial b}(t, \boldsymbol{Y}(t, b) \,|\, b) + \nabla_{\boldsymbol{Y}} \boldsymbol{f} \cdot \boldsymbol{S}(t, b).$$

We have

$$\frac{\partial \boldsymbol{f}}{\partial b}(t, \boldsymbol{Y}(t, b) \,|\, b) = \begin{pmatrix} 0 \\ 0 \\ 2\theta p_O A_O \\ 0 \end{pmatrix}, \quad \text{and} \quad \nabla_{\boldsymbol{Y}} \boldsymbol{f} = \begin{pmatrix} -a_R & p_R & 0 & 0 \\ a_R & -p_R & 0 & 0 \\ 0 & p_R & -a_O & 2\theta b p_O \\ 0 & 0 & a_O & -p_O \end{pmatrix}.$$

Solving for the $2n$ variables simultaneously, we take advantage of the generous form of the coupled system due to linearity. Let $\boldsymbol{X}$ denote the vector $(y_1, \dots, y_n, S_1, \dots, S_n) \in \mathbb{R}^{2n}$, then, $\boldsymbol{X}$ satisfies

$$\frac{d\boldsymbol{X}}{dt}(t) = (I_2 \otimes \nabla_{\boldsymbol{Y}} \boldsymbol{f} + L_2 \otimes \boldsymbol{A}) \cdot \boldsymbol{X}(t)$$

with the notation

$$I_2 = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}, \qquad L_2 = \begin{pmatrix} 0 & 0 \\ 1 & 0 \end{pmatrix},$$

and $\boldsymbol{A}$ is the matrix whose elements are defined by

$$\boldsymbol{A}_{ij} = \frac{\partial}{\partial y_j}\frac{\partial f_i}{\partial b} + \left(\frac{\partial}{\partial y_j}\nabla_{\boldsymbol{Y}} \boldsymbol{f}\right) \cdot S_i.$$

Take-home message information

Successes:

- Feedback-sensitive mechanistic ODE model inspired by a state-of-the-art models for mouse + proof of nice properties.
- Implementation of various scenarii and classification of most fitting feedbacks for the fish system.
- Preprint ready for submission (Hydra Morphallaxis) + New theorems.
- Sensitivity analysis pipeline developped for further steps.

To-do:

- Find best transformation of available data for integration in the parameter fitting routine.
- Design new experiments designed for this project.
- Explore variations of the model and response to injury.

Thank you for you attention!

Questions?

References I