UNIVERSITÄT
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SEIT 1386

Modeling Zebrafish's Adult Neural Stem Cell Dynamics with Feedback

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Introduction

Neural Stem Cells (NSC) are a specialized population of cells with the ability to self-renew and differentiate into various neural lineages, such as neurons and glial cells.

In adult mice, the SGZ and SVZ are the main neurogenic territories, and it is observed that the number of NSCs declines with age in these regions.

In adult zebrafish, NSCs are predominantly located in the telencephalon, where they maintain lifelong neurogenic activity.

It is thought that lifelong neurogenic potential of adult zebrafish arise from a finely tuned regulation of stem cell fate dynamics (i.e., how these cells stay active, grow, and turn into other cell types).

Question

How do regulatory mechanisms governing NSC fate contribute to the maintenance of NSC populations in adult zebrafish, and how to model them mathematically?

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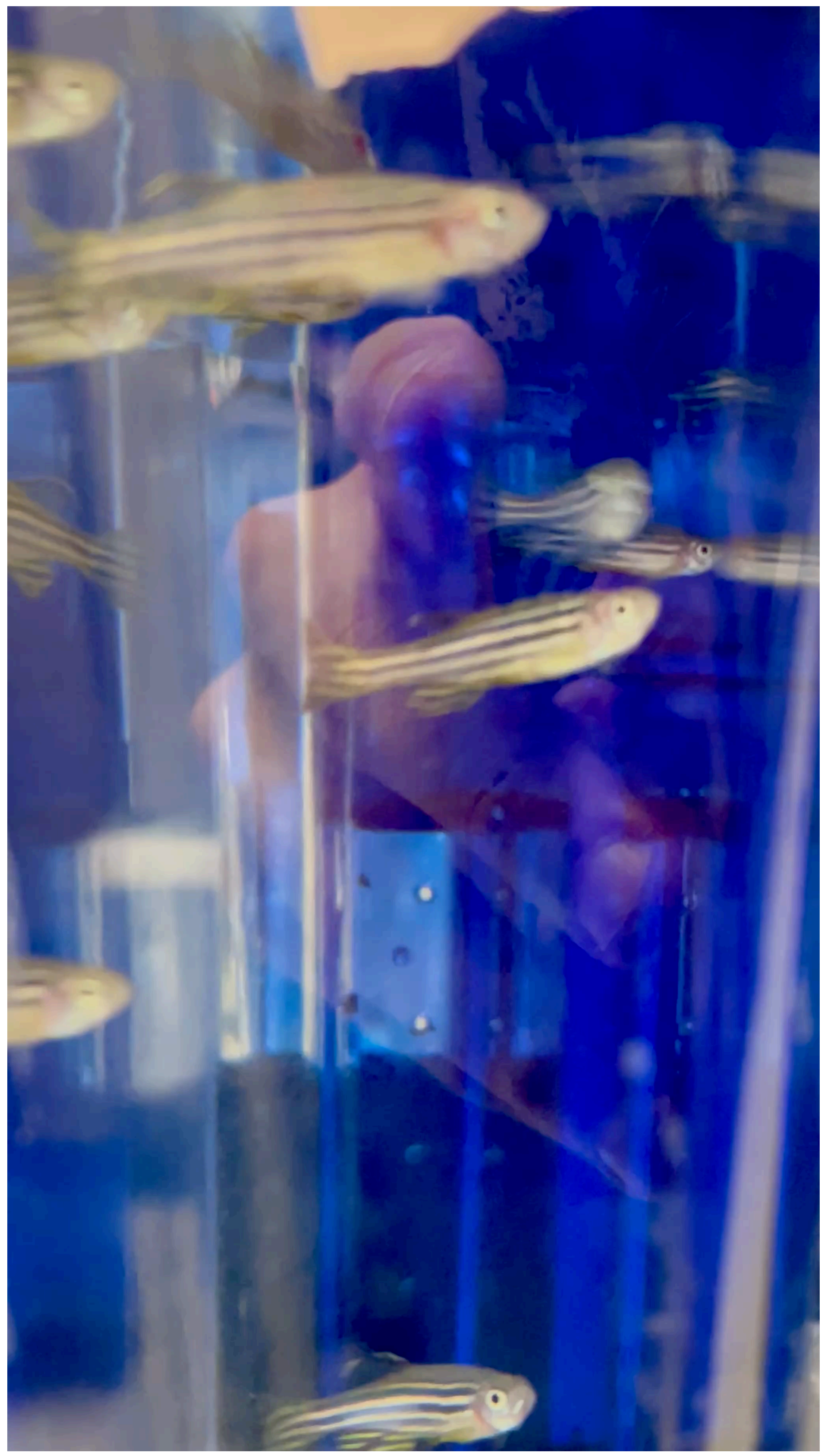
Introduction II

Wild Type



Introduction II

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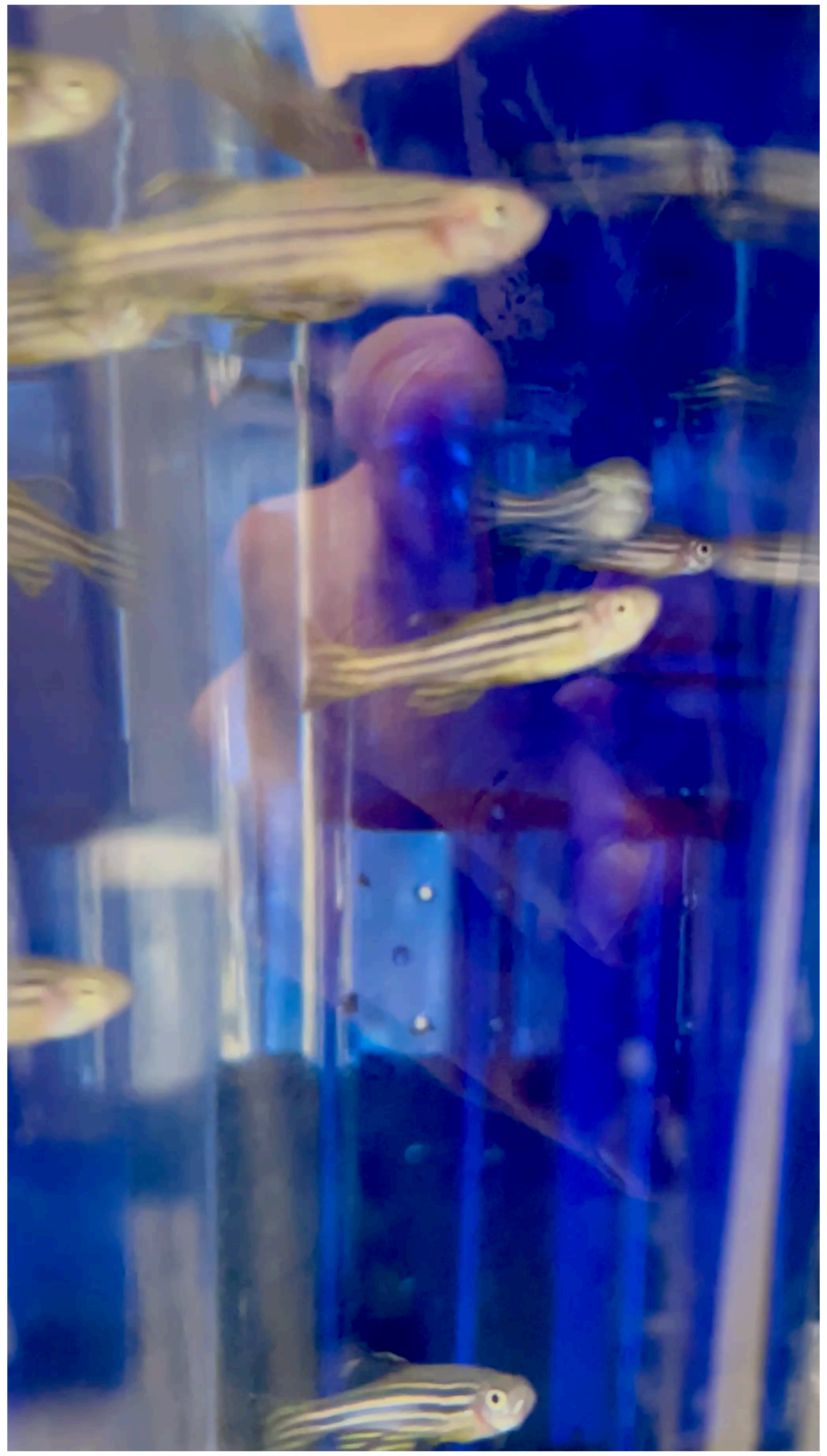

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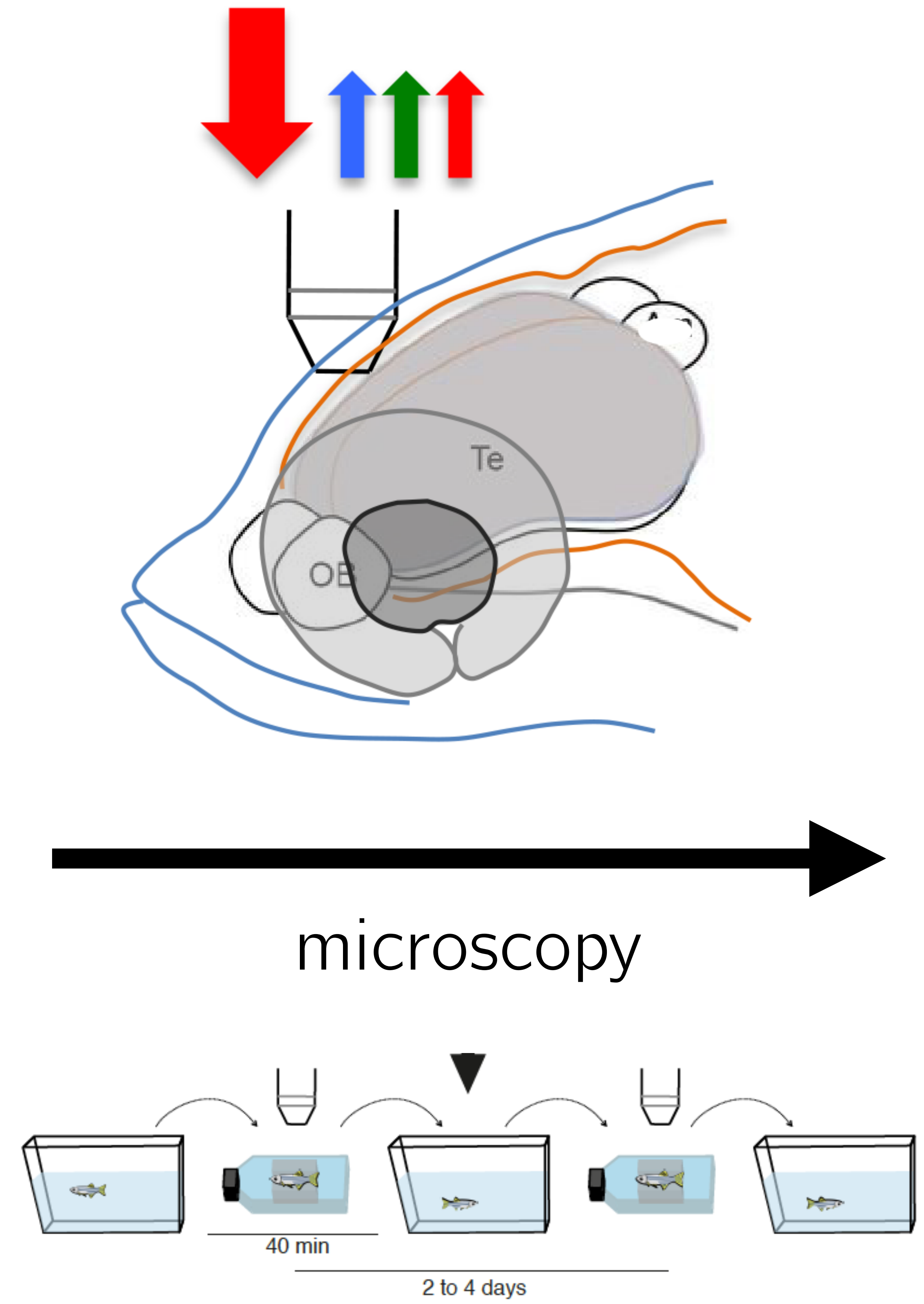
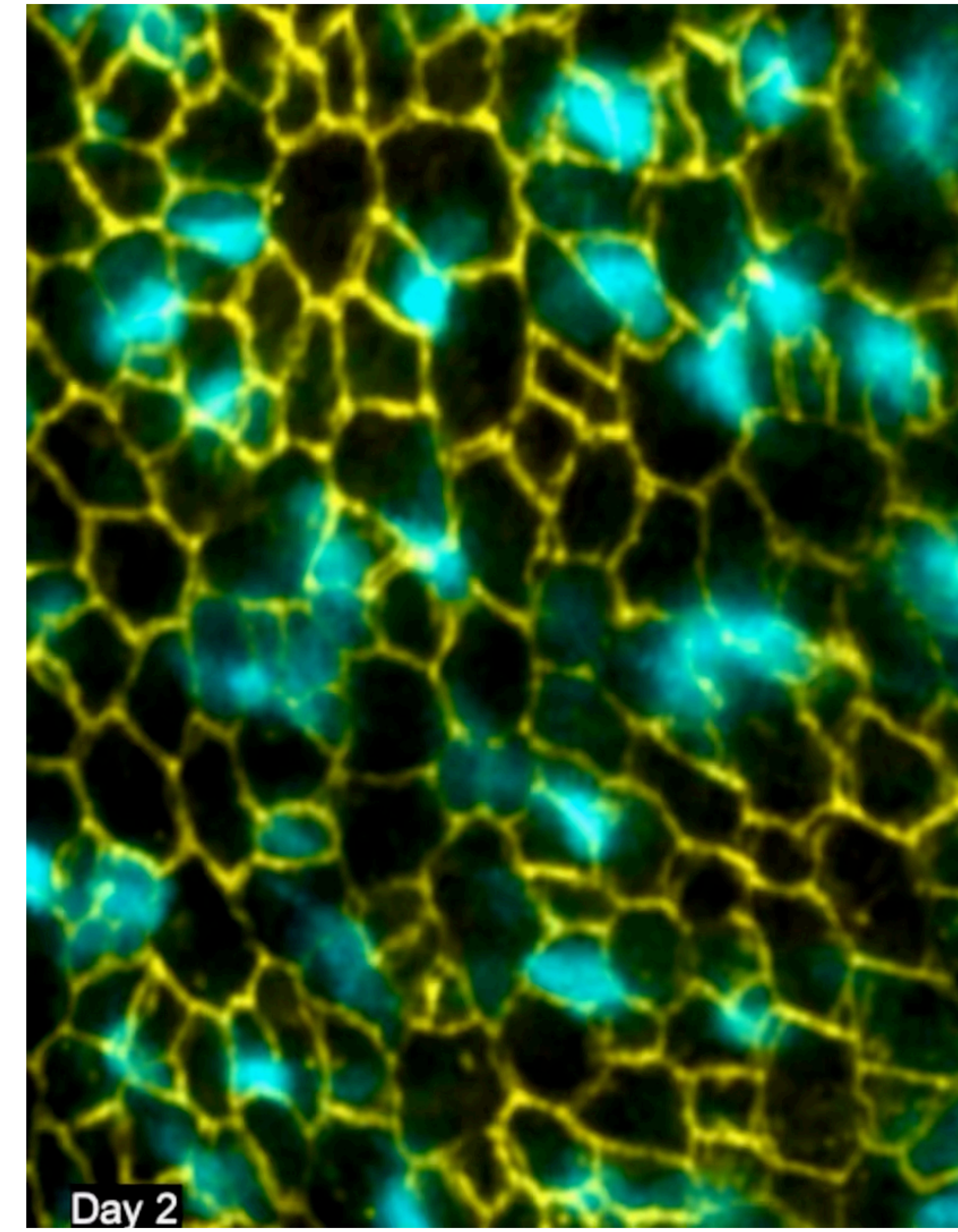
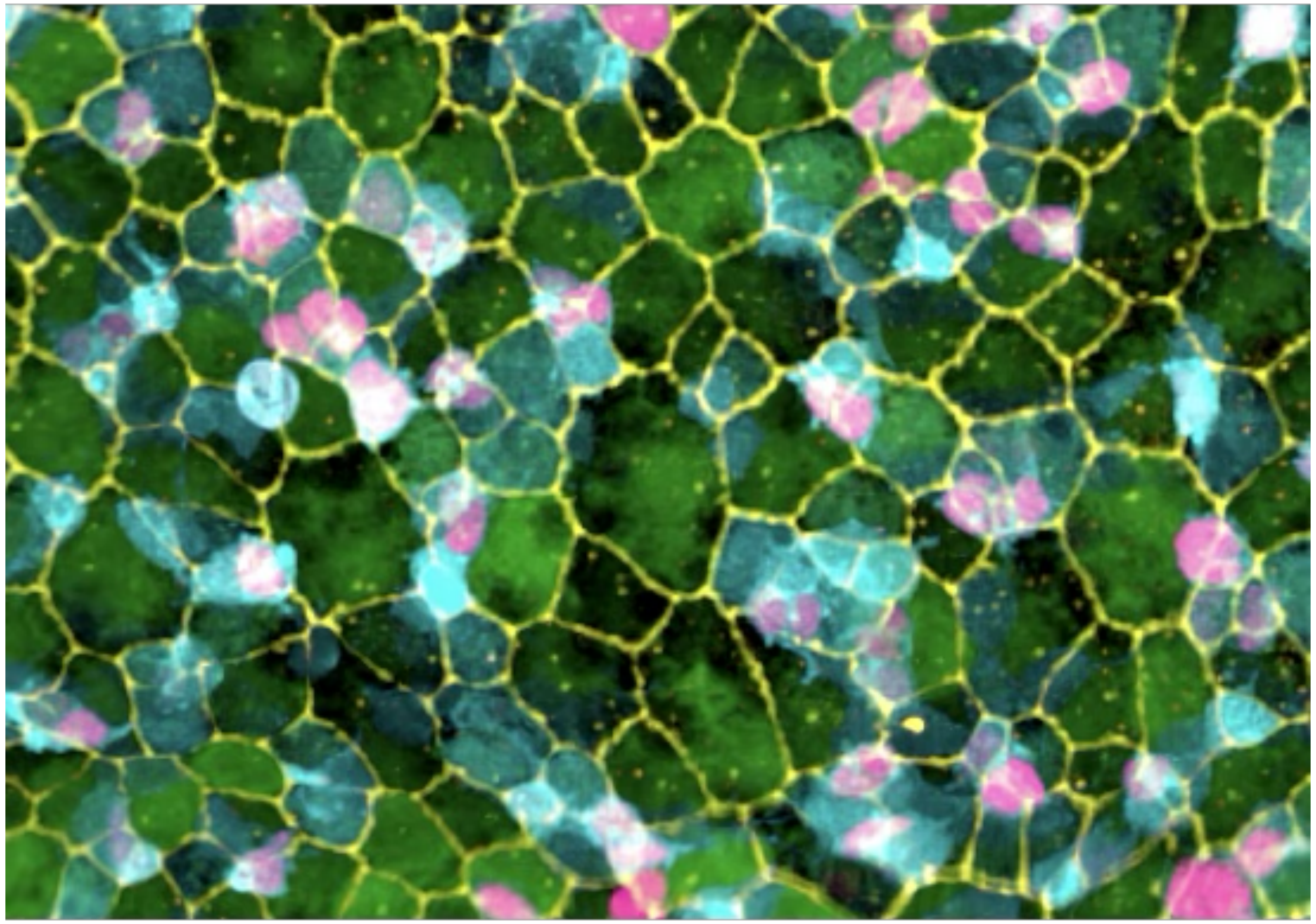


In Vivo Movie

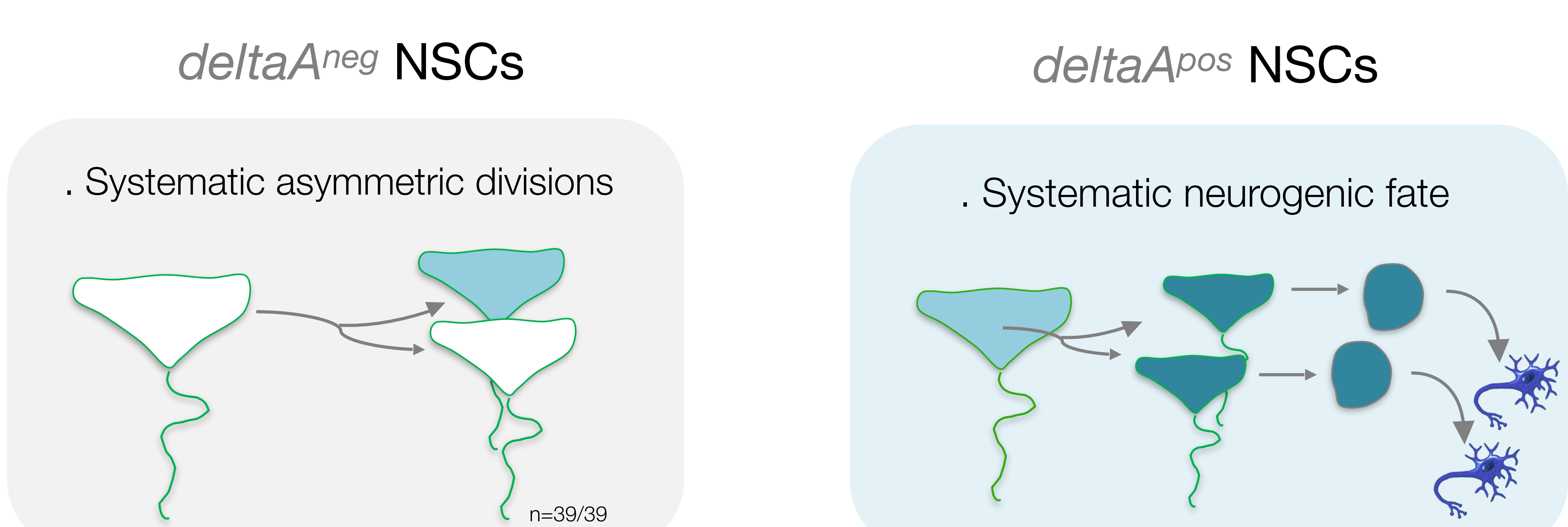


Multiple time points per individual $\Longrightarrow$ much less measurement noise than in mice!

Introduction III



Green: GFAP   Magenta: PCNA   Cyan: deltaA

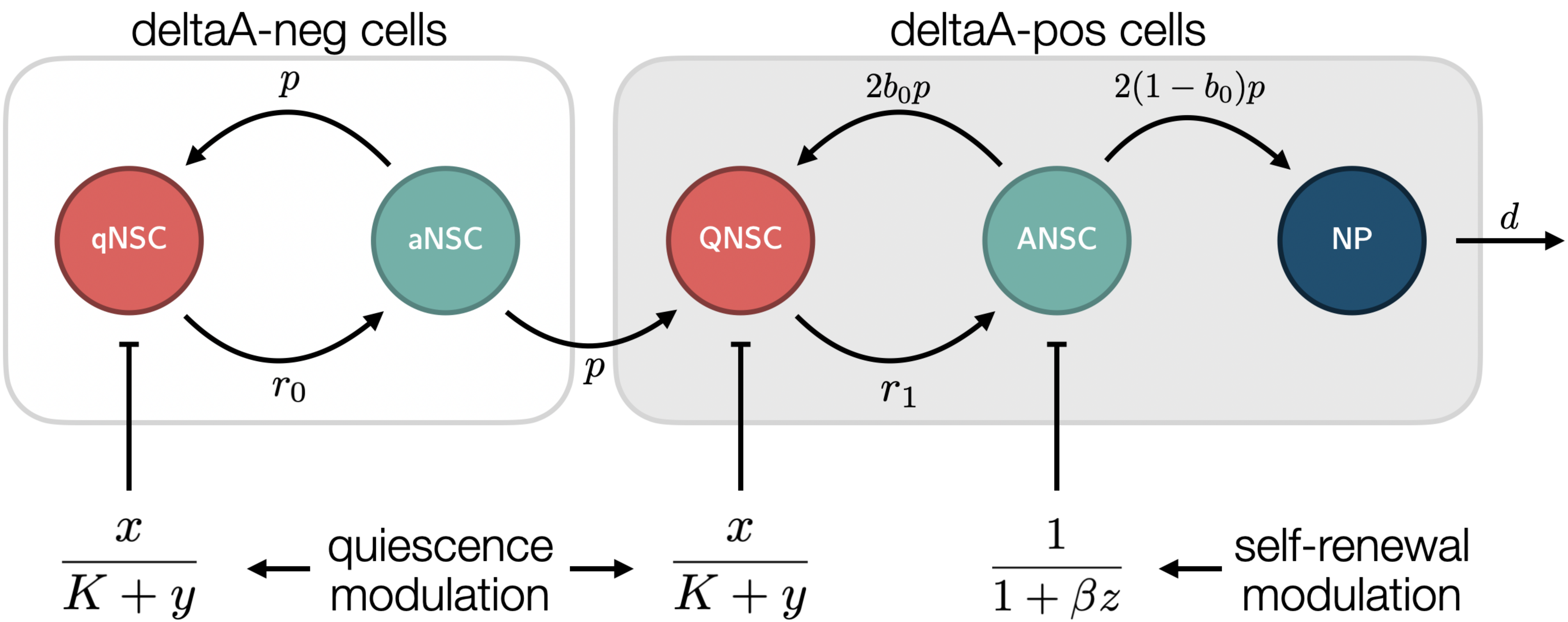


In the zebrafish Telencephalon, the NSC population is highlighted using the cell marker Sox2.

Five subtypes are detected and optically segregated using three additional markers.

	GFAP	PCNA	deltaA
qNSC	+	−	−
aNSC	+	+	−
QNSC	+	−	+
ANSC	+	+	+
NP	−	−	+

Introduction IV



Model Equations

- System equations

$$
\begin{cases}
q'(t) = -r_0 \dfrac{x(t)}{K + y(t)} q(t) + pa(t), \\
a'(t) = \quad r_0 \dfrac{x(t)}{K + y(t)} q(t) - pa(t), \\
Q'(t) = -r_1 \dfrac{x(t)}{K + y(t)} Q(t) + 2 \dfrac{b_0}{1 + \beta z(t)} pA(t) + pa(t), \\
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P'(t) = \quad 2 \left(1 - \dfrac{b_0}{1 + \beta z(t)}\right) pA(t) - dP(t),
\end{cases}
\qquad +\text{init. cond.}
$$

- State variables: q, a, Q, A, P (qNSC, aNSC, QNSC, ANSC, and NP respectively)
- Total parameters: $r_0, r_1, b_0, p, d, K, \beta$
- Feedback functions: $S_1(x, y) = \frac{x(t)}{K+y(t)}$, $\quad S_2(z) = \frac{1}{1+\beta z(t)}$

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Existence of a global solution

Since the RHS is Lipschitz-continuous, we use Picard-Lindelöf theorem to obtain local existence of a solution on a maximal interval $I_{\max} := [0, T_{\max})$.

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Positivity Criterion

Consider the n-dimensional IVP $\dot{\boldsymbol{x}} = \boldsymbol{f}(\boldsymbol{x}); \boldsymbol{x}(0) = \boldsymbol{x}_0$, with state vector $\boldsymbol{x} = (x_1, ..., x_n)$, initial condition $\boldsymbol{x}_0 \in \mathbb{R}^n_+$, and RHS $\boldsymbol{f} = (f_1, \dots, f_n) : \mathbb{R}^n \to \mathbb{R}^n$. If the function $\boldsymbol{f}$ has the property

$$\forall \boldsymbol{x} \in \mathbb{R}^n_+, \quad (x_k = 0) \implies (f_k(\boldsymbol{x}) \geq 0),$$

then $\mathbb{R}^n_+$ is an invariant set of the system, i.e., any solution with non-negative initial condition $\boldsymbol{x}_0 \geq 0$ will stay non-negative for all times $t \in [0, T_{\max})$.

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The RHS of our system satisfies the positivity criterion, hence we can guarantee the non-negativity of solutions with non-negative initial condition.

Existence of a global solution II

- We have $(q+a)' = 0$, so the sum $q + a = \theta$, where we defined $\theta := q_0 + a_0$. Since both terms are positive and their sum is bounded, we get the estimates $0 \le q, a \le \theta$.

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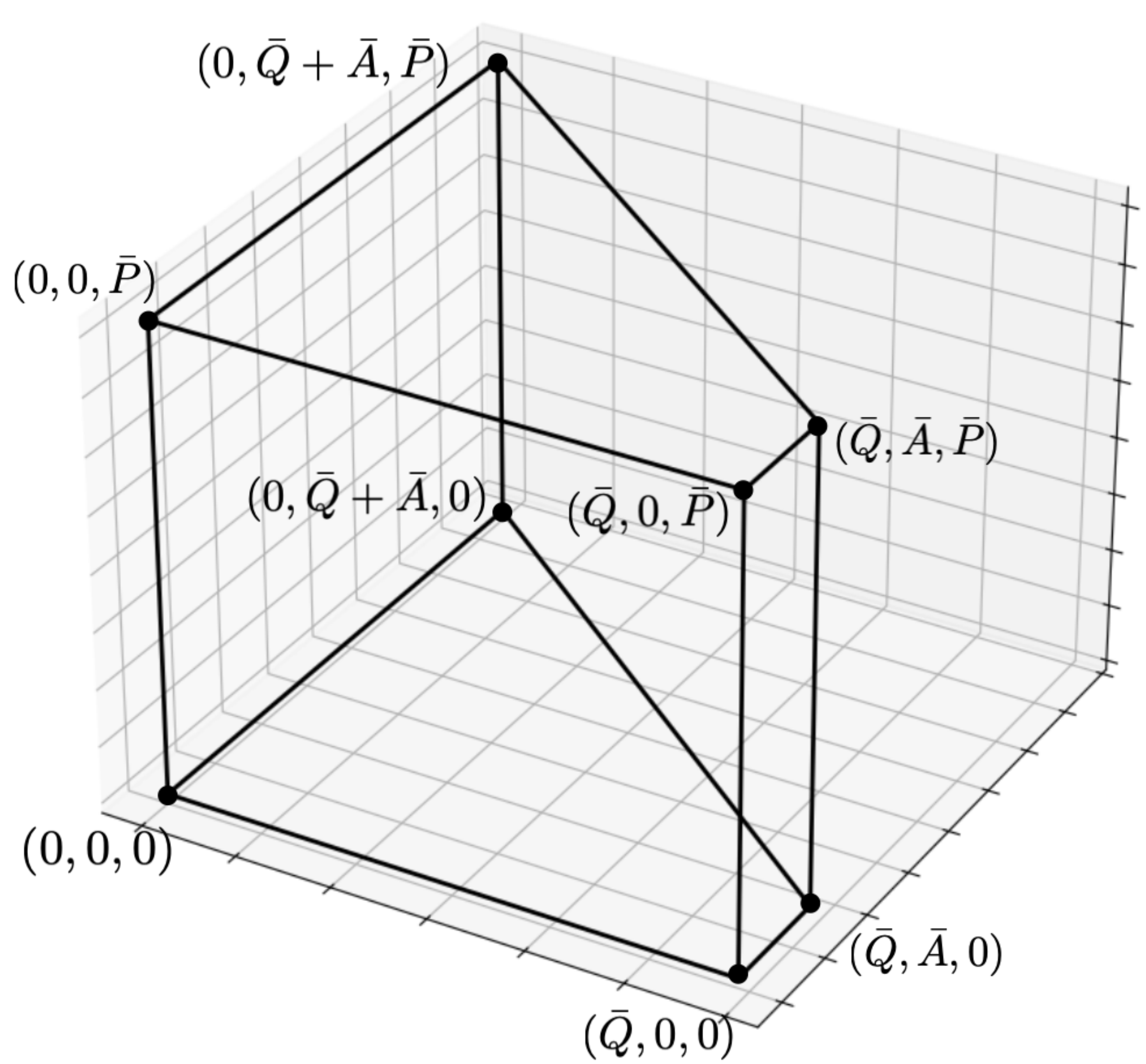
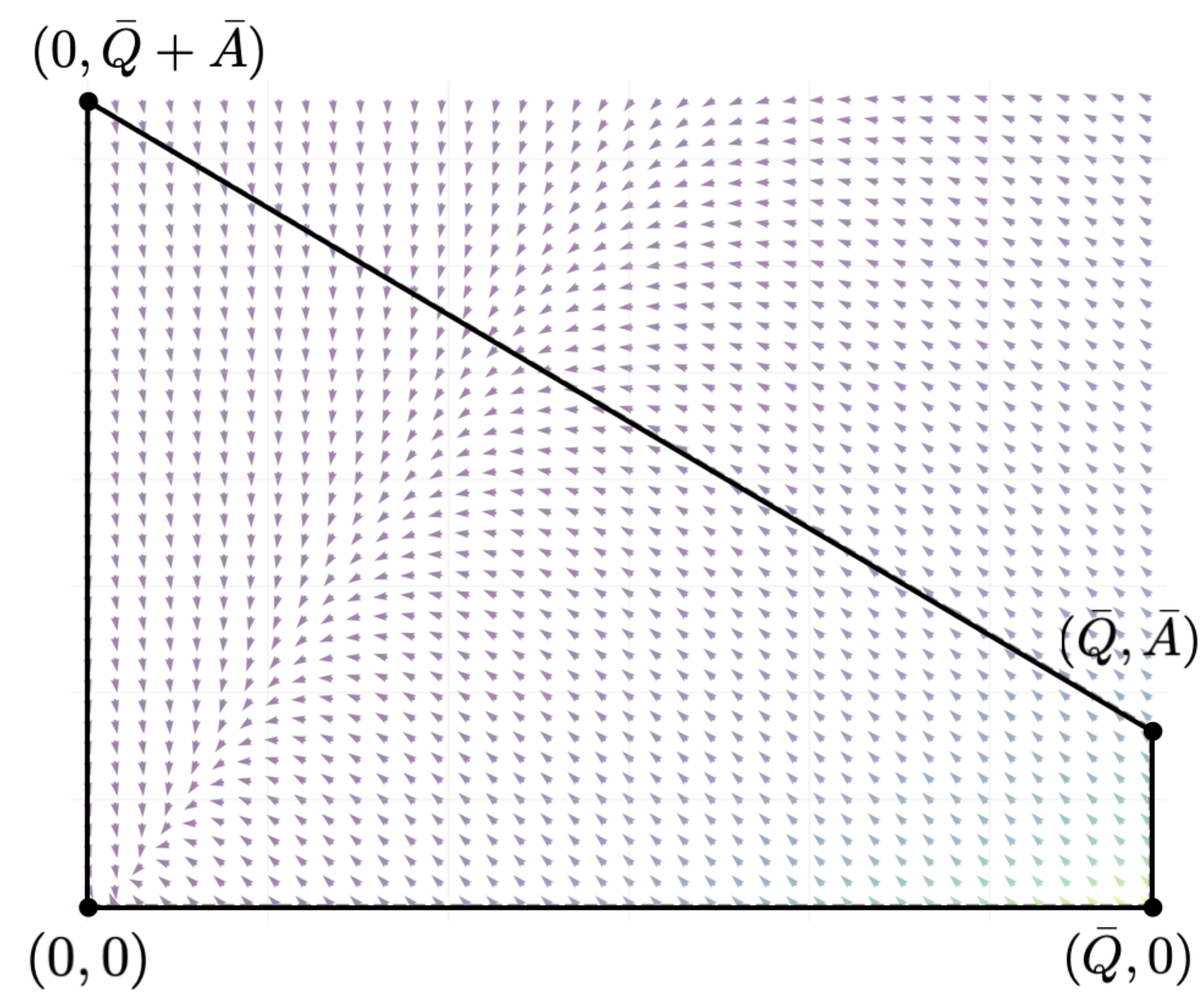
- It is possible to trap Q, A and P inside the 3d-trapezoidal region (left)

3-dimensional region



cross-section + vector field



Existence of a global solution III

Theorem (Invariant set)

Let $\varepsilon > 0$ *and introduce the following quantities*

- $\bar{Q} := \sqrt{\frac{p(K+\bar{A})(2b_0\bar{A}+\theta)}{r_1}} + \varepsilon,$
- $\bar{A} := \frac{\theta}{1-2b_0} + \varepsilon,$
- $\bar{P} := \frac{2p\bar{A}}{d} + \varepsilon$
- $T := \mathrm{Hull}\{(0,0),(\bar{Q},0),(\bar{Q},\bar{A}),(0,\bar{Q}+\bar{A})\},$

Then, the region $\Sigma := [0,\theta]^2 \times \overline{T} \times \left[0,\bar{P}\right]$ *is an invariant set for the qaQAP system.*

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Proof;

1. $(q,a) \in [0,\theta]^2$ is trivial.
2. from $\frac{d}{dt}(Q+A)|_{A=\bar{A}} = pa - \left(1 - \frac{2b_0}{1+\beta P}\right) p\bar{A}$, find $\bar{A}$ s.t. $(Q+A)' < 0$
3. from $Q'|_{Q=\bar{Q}} = -r_1 \frac{\bar{Q}^2}{K+A} + 2\frac{b_0}{1+\beta P} + pa$ solve for $\bar{Q}$ s.t. $Q' < 0$ (same for $\bar{P}$).
4. Check the gradient condition on all six faces of Σ.

$\square$

Steady states

Solving for the non-trivial root of the steady state equation $F(q, a, Q, A, P) = 0$ is a complex task. Three methods have been tested:

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- Compute q, a, Q, A, P as functions of the signaling, and solve the algebraic equation (works, fast)

$$q^*(s_1, s_2) = \frac{\theta p}{p + r_0 s_1}$$

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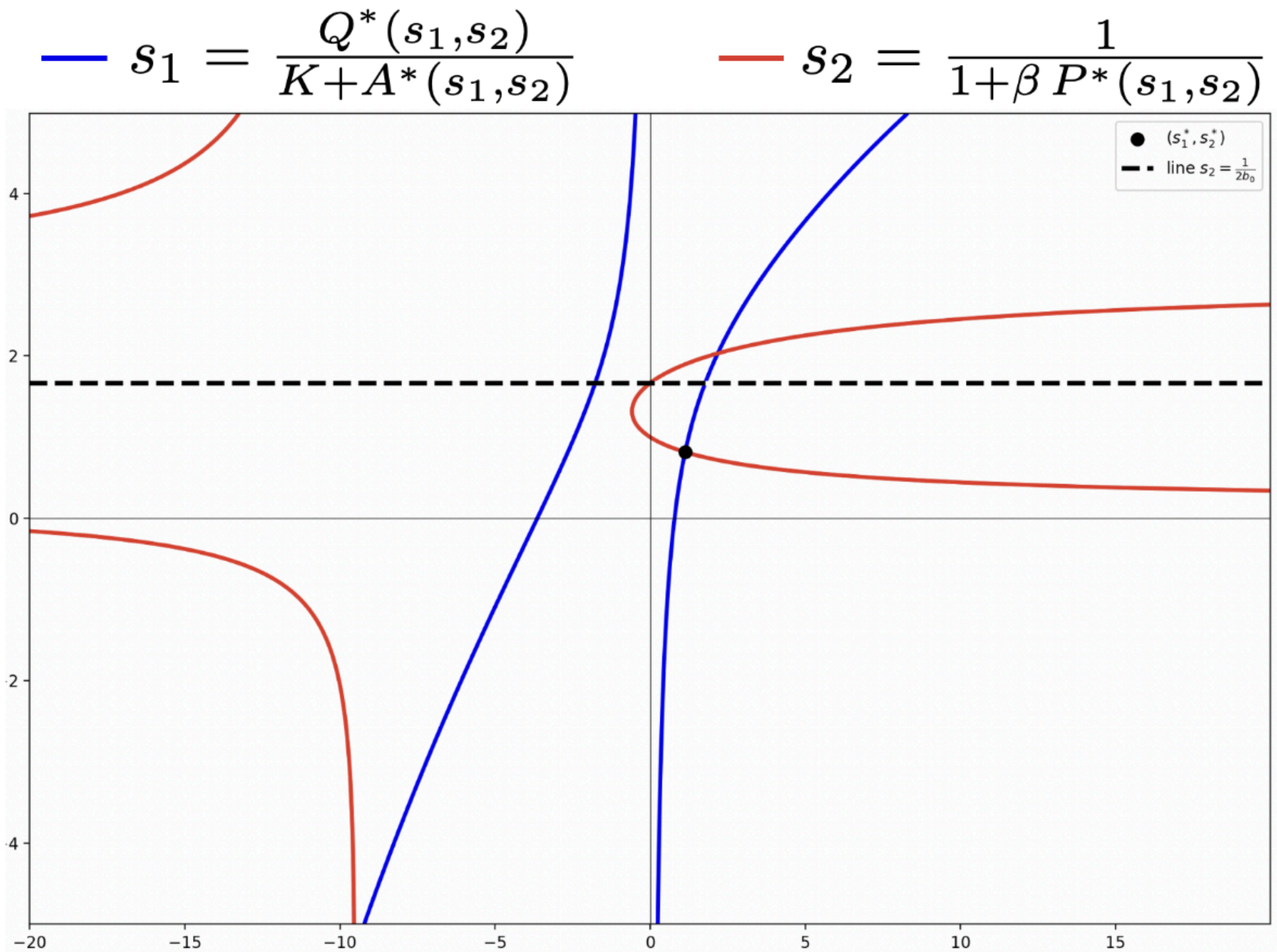


Steady states II

Use $q = \theta - a$ to kick one equation out, write $v = \theta^{-1} a$. The Jacobian of the system in the new coordinates (v, Q, A, P) reads as

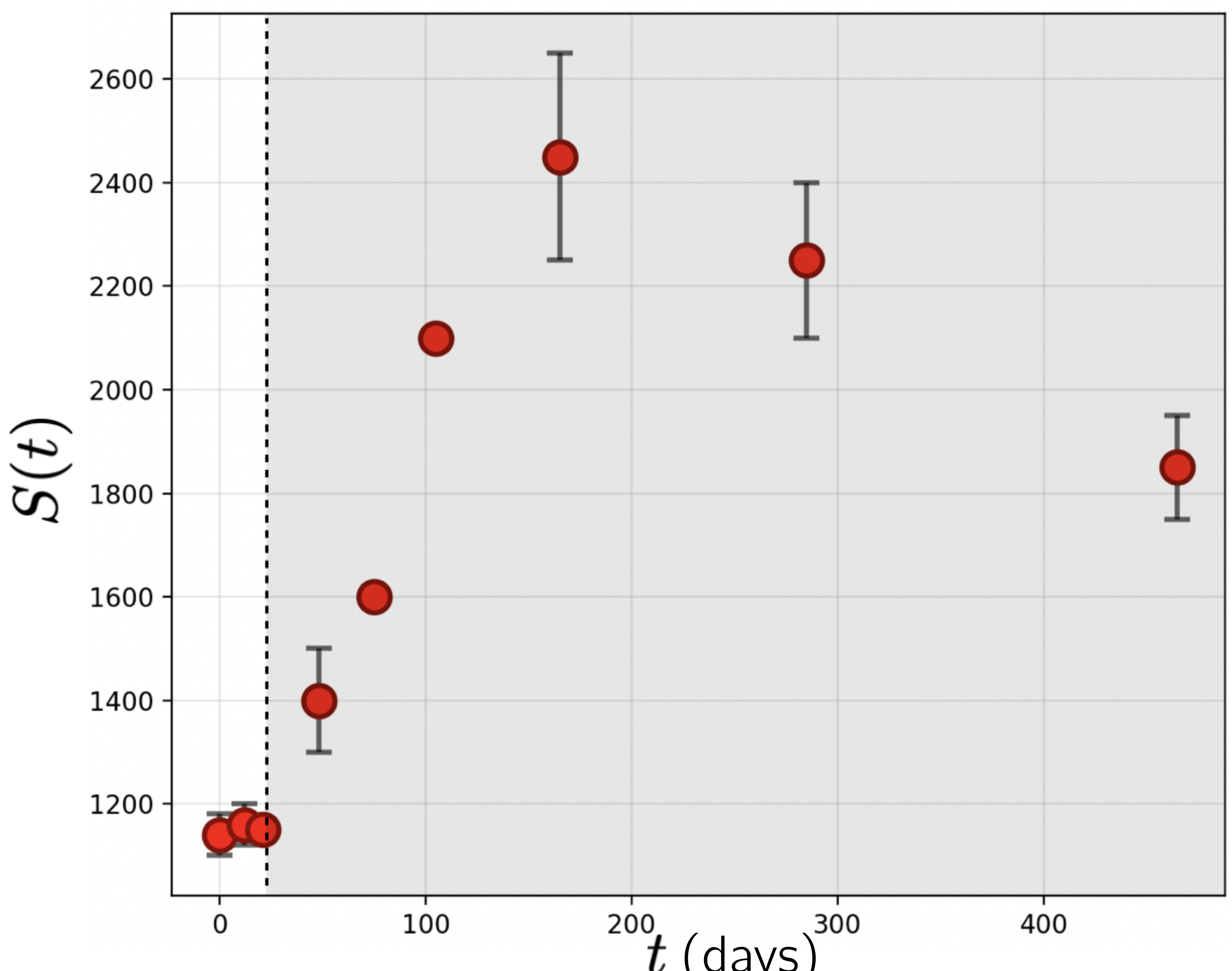
$$J(v,Q,A,P) = \begin{bmatrix} -\left(p + r_0 \dfrac{Q}{K+A}\right) & \dfrac{r_0(1-v)}{K+A} & -\dfrac{(1-v)r_0 Q}{(K+A)^2} & 0 \\ p\theta & -\dfrac{2r_1 Q}{K+A} & \dfrac{r_1 Q^2}{(K+A)^2} + \dfrac{2b_0 p}{1+\beta P} & -\dfrac{2b_0 \beta p A}{(1+\beta P)^2} \\ 0 & \dfrac{2r_1 Q}{K+A} & -p & 0 \\ 0 & 0 & 2p\left(1 - \dfrac{b_0}{1+\beta P}\right) & \dfrac{2b_0 \beta p A}{(1+\beta P)^2} - d \end{bmatrix}$$

Numerical perturbation analysis of the steady state shows that there exists $\boldsymbol{\varepsilon} > 0$ s.t. $s(J(\boldsymbol{x}^*(\boldsymbol{\varrho} + \boldsymbol{\varepsilon} \odot \tilde{\boldsymbol{\varrho}})) < 0$, for all $\tilde{\boldsymbol{\varrho}} \in B(0,1)^7$. Steady state is stable modulo a small perturbation.

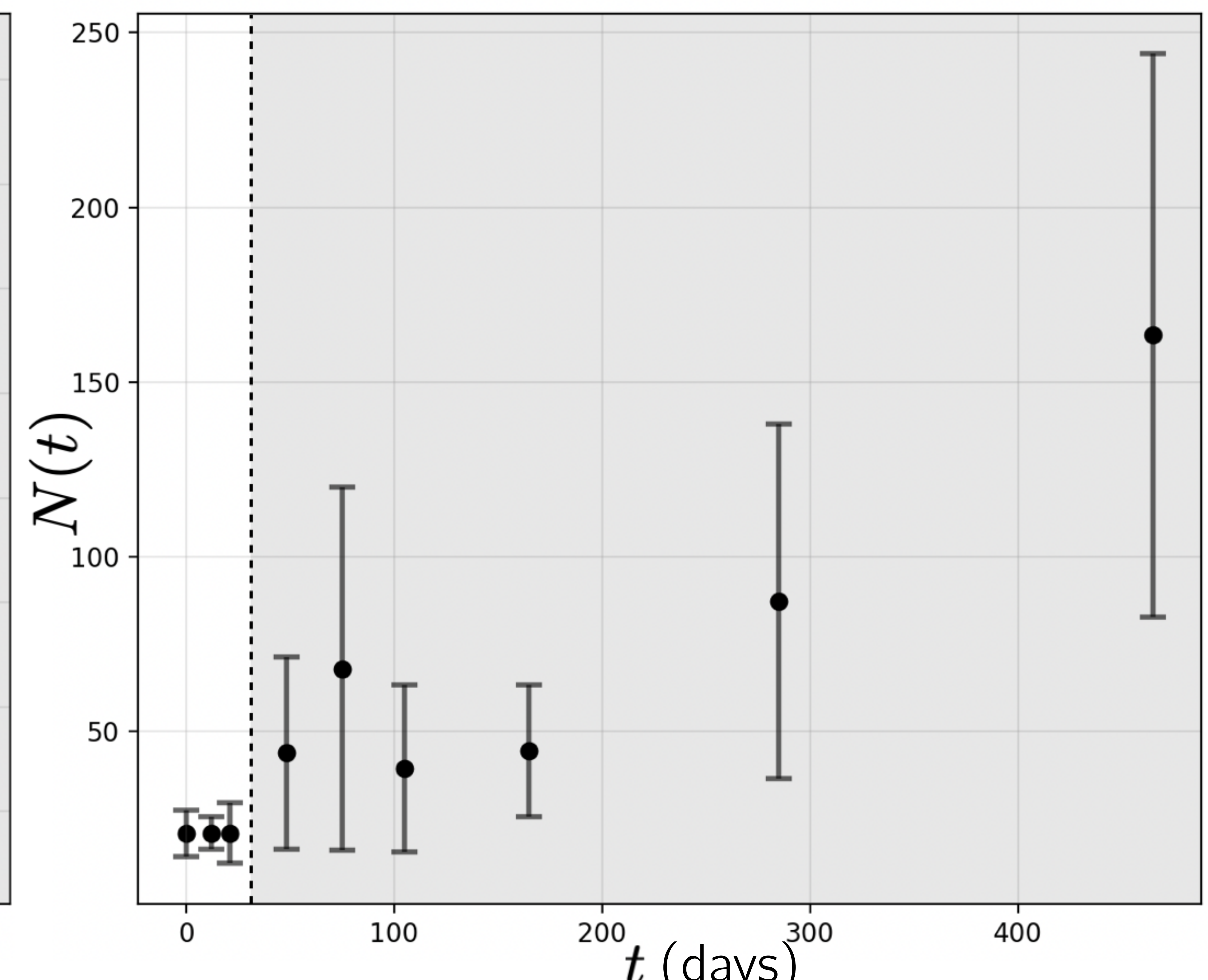
A look at the data

- Two data sets available to us. The zero time point = 3mpf (start of fish adulthood).
- New dynamics observed at 4mpf: population grows due to an upstream source effect.

Total population
$$S(t) = (q + a + Q + A + P)(t)$$



Neurons $N(t) = N(0) + \int_0^t \nu P(s)ds$



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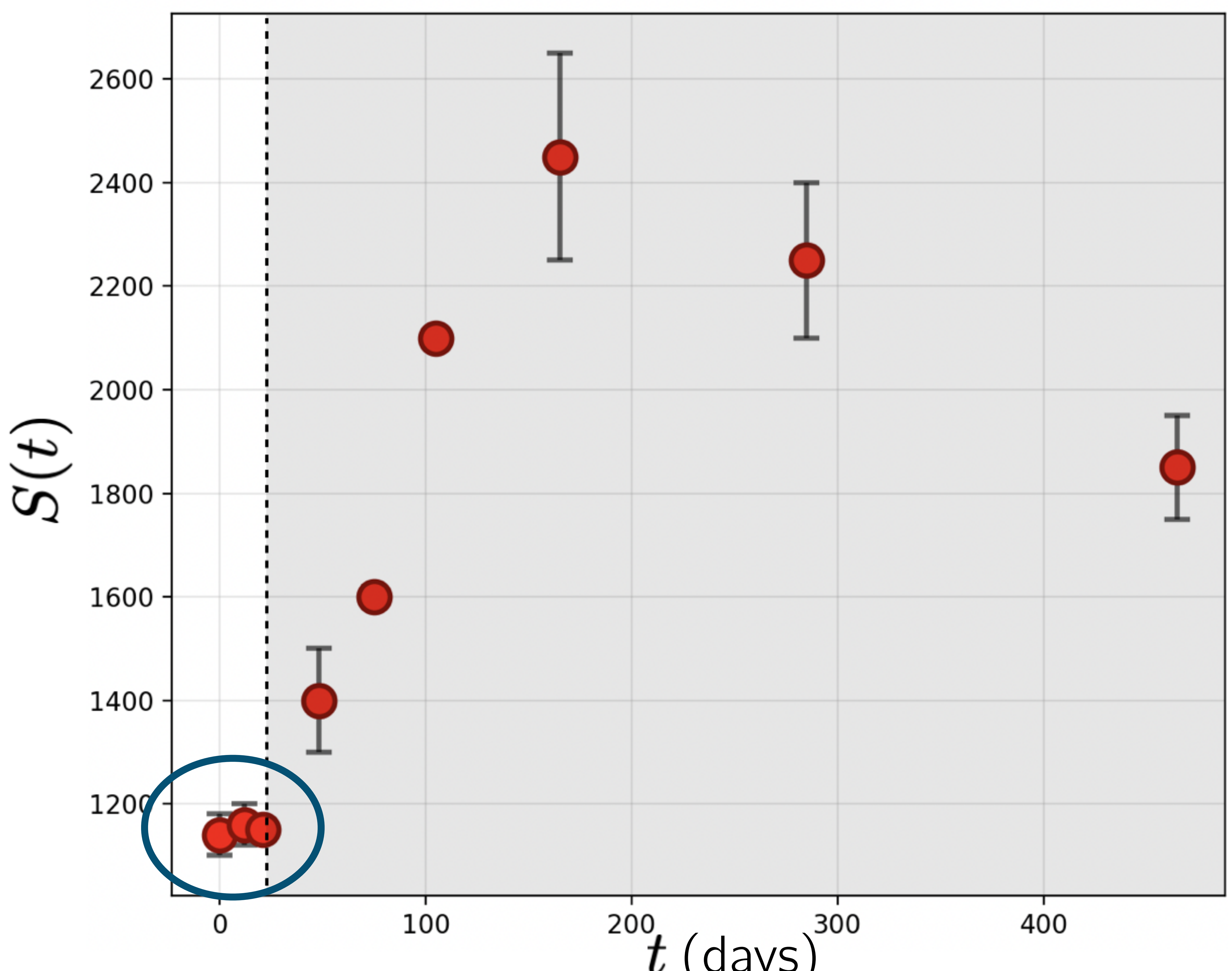

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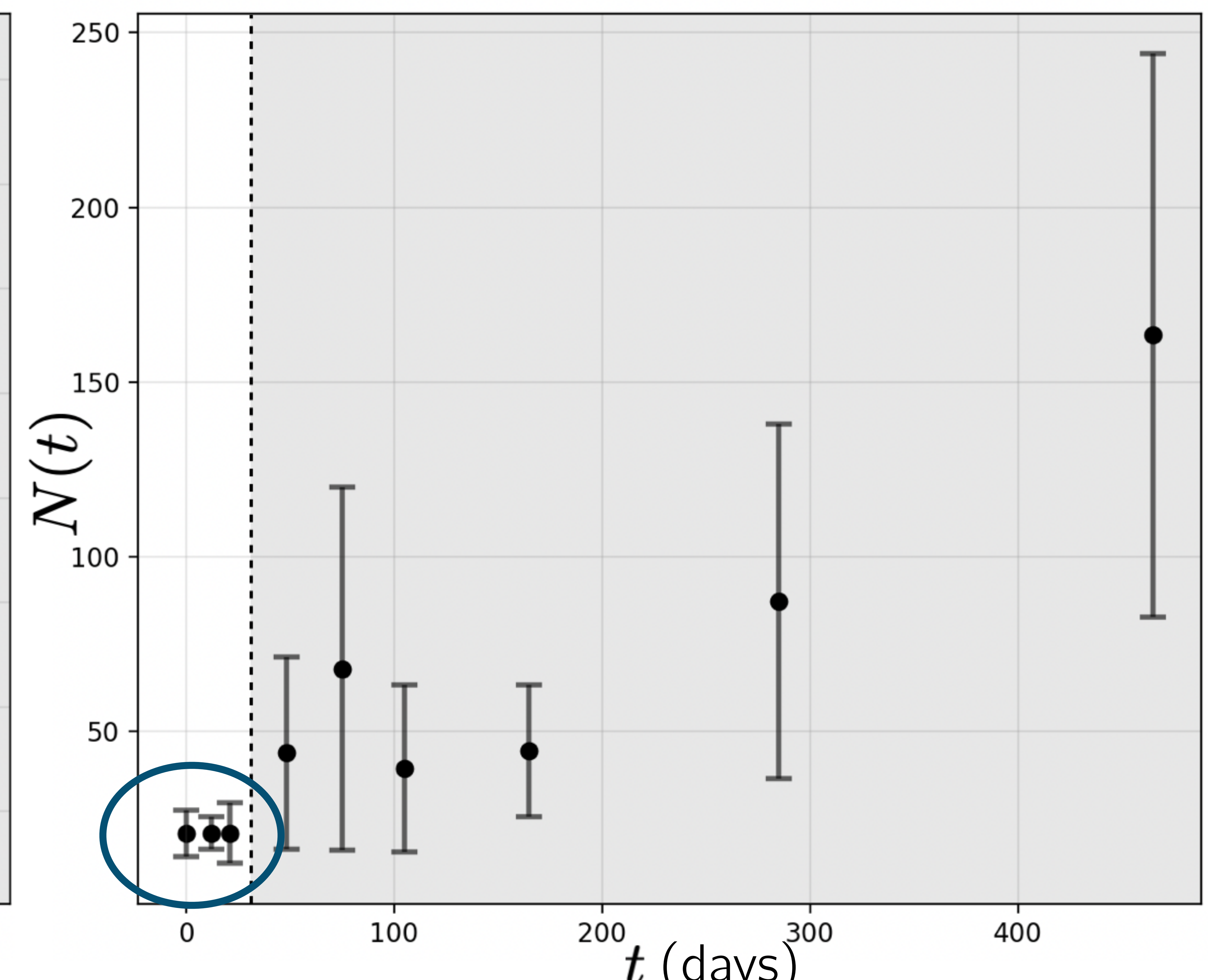

A look at the data II

- From [papers], we obtain $S^* = 1150$, and

$$\frac{q^*}{q^* + Q^*} = 0.77, \quad \frac{A^*}{a^* + A^*} = 0.87, \quad \frac{q^* + Q^*}{S^*} = 0.82, \quad \frac{a^* + A^*}{S^*} = 0.05, \quad \frac{P^*}{S^*} = 0.13.$$

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- Isolate each proportion:

$$q^* = S^* \times \left(\frac{q^*}{q^* + Q^*}\right) \times \left(\frac{q^* + Q^*}{S^*}\right) = 726.11, \quad \text{(do the same for } a^*, Q^*, A^*, P^* \text{...)}$$

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- Four parameters eliminated from the system using:

$$r_0(p, K, \beta) = \frac{pA^*(K + A^*)}{q^* Q^*} \qquad r_1(p, K, \beta) = \frac{pA^*(K + A^*)}{(Q^*)^2}$$

$$b_0(p, K, \beta) = \frac{1 + \beta P^*}{2}\left(1 - \frac{a^*}{A^*}\right) \qquad d(p, K, \beta) = \frac{p(a^* + A^*)}{P^*}$$

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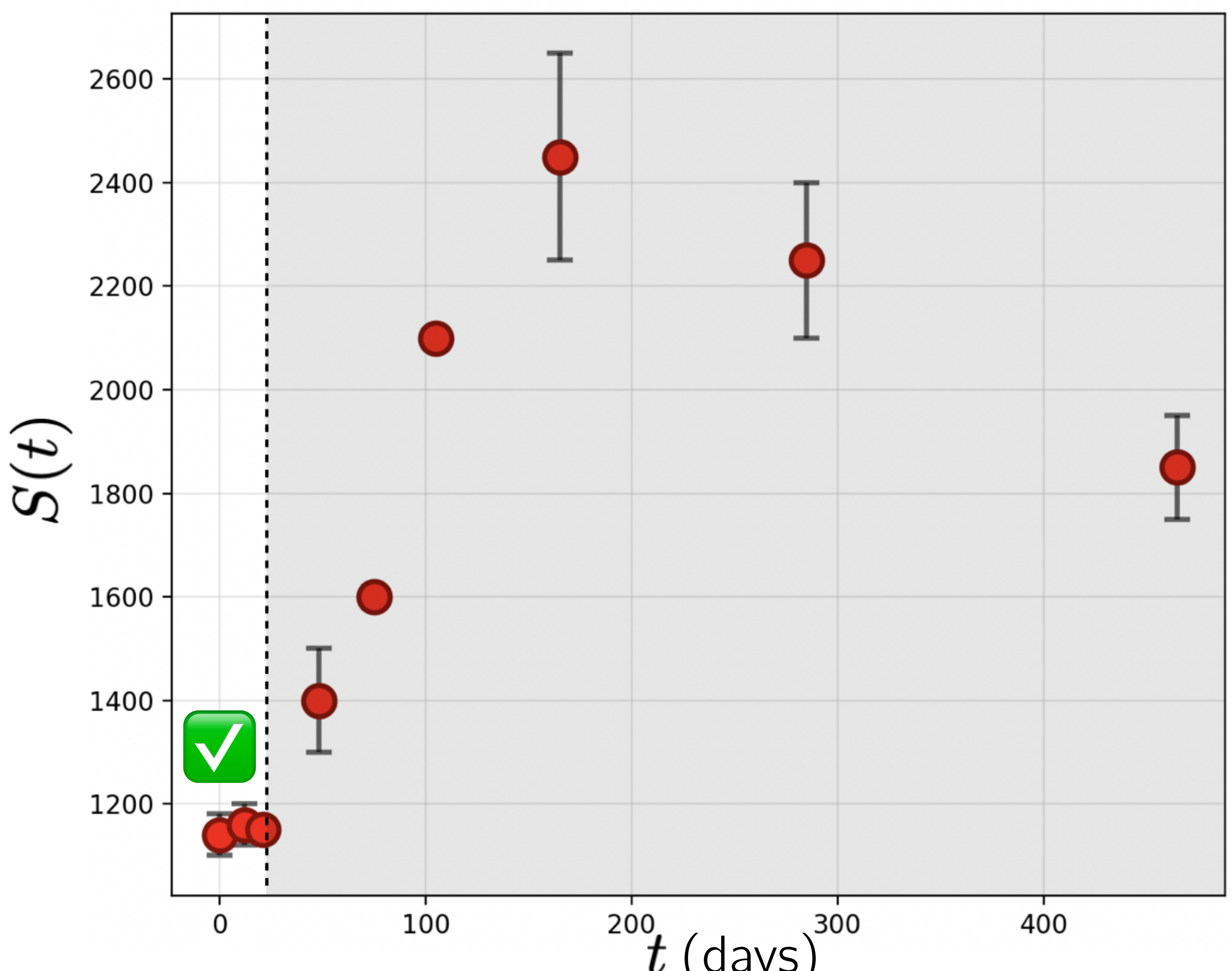

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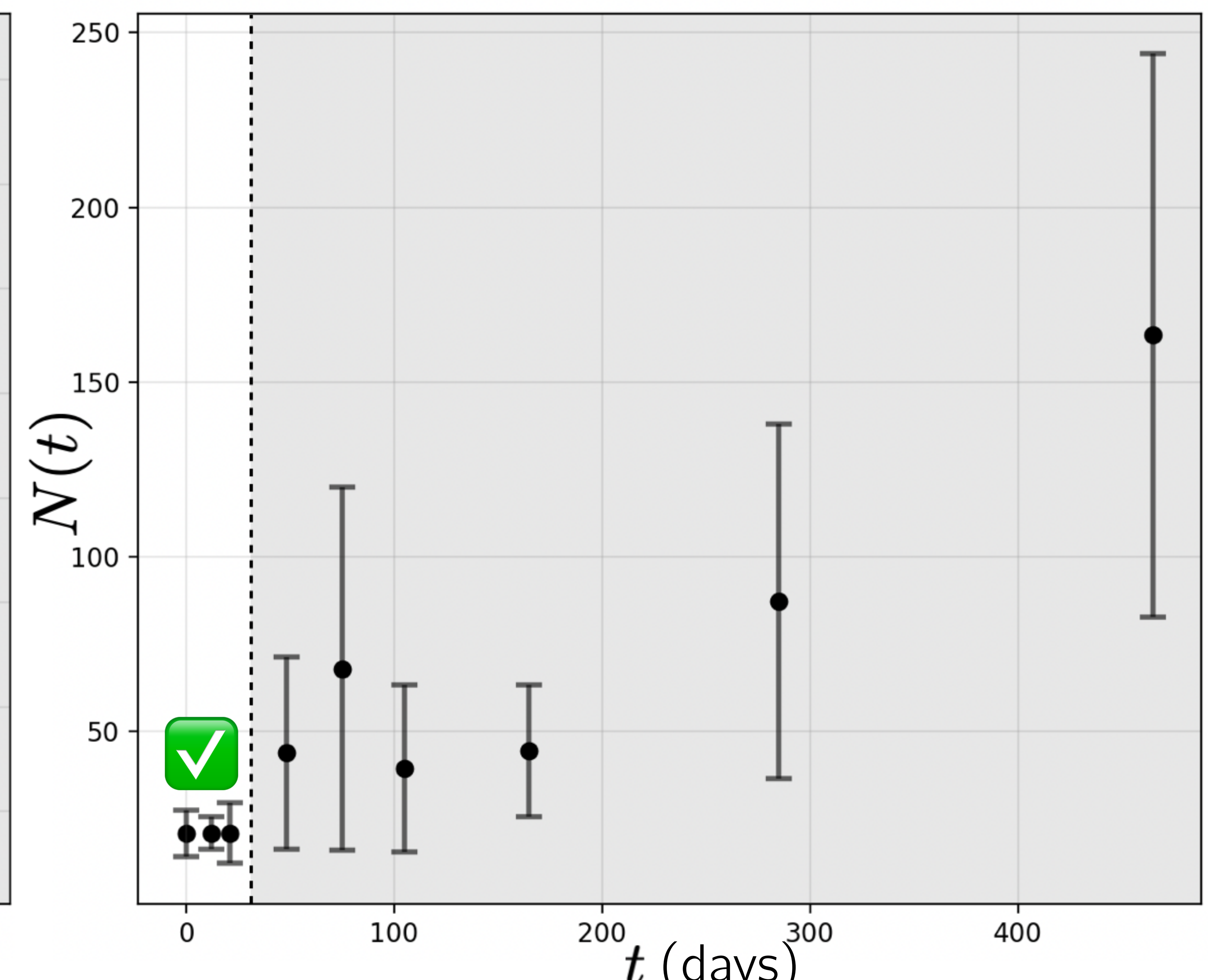

Adding the source

Model the source by introducing self-renewal in deltaA-neg NSCs dynamics:

$$\begin{cases} q'(t) = -r_0 \dfrac{Q(t)}{K + A(t)} q(t) + \dfrac{2\gamma}{1+\alpha P} p a(t), \\ a'(t) = \quad r_0 \dfrac{Q(t)}{K + A(t)} q(t) - p a(t), \\ Q'(t) = -r_1 \dfrac{Q(t)}{K + A(t)} Q(t) + 2 \dfrac{b_0}{1 + \beta P(t)} p A(t) + 2 \left(1 - \dfrac{\gamma}{1+\alpha P}\right) p a(t), \qquad +\text{init. cond.} \\ A'(t) = \quad r_1 \dfrac{Q(t)}{K + A(t)} Q(t) - p A(t), \\ P'(t) = \quad 2 \left(1 - \dfrac{b_0}{1 + \beta P(t)}\right) p A(t) - d P(t), \end{cases}$$

Total parameters: $p, K, \beta, \gamma, \alpha$ (r_0, r_1, b_0, d fixed, computed from p, K, β.)

Fitting ODEs to data II

By monotony of the logarithm function, maximizing the likelihood is equivalent to maximizing the log-likelihood $\mathcal{LL}(\varrho) := \log \mathcal{L}(\varrho)$ over $\varrho \in \mathcal{P}$. Expanding the definition, the log-likelihood reads as

$$\mathcal{LL}(\varrho) := -\frac{n}{2}\log(2\pi) - \sum_{i=1}^{n} \log(\sigma_i^2) - \underbrace{\frac{1}{2}\sum_{i=1}^{n} \frac{\left(\eta_i - h_i(t_i, \boldsymbol{y}(t_i;\varrho), \varrho)\right)^2}{\sigma_i^2}}_{\text{only this term depends on } \varrho \text{ !}}.$$

Optimization problem

The parameter vector ϱ that maximizes the likelihood is expressed as the solution to the Nonlinear Least-Squares (NLS) problem:

$$\text{find } \bar{\varrho} \text{ such that } \qquad \bar{\varrho} := \operatorname{argmin}_{\varrho \in \mathcal{P}} \left\{ \frac{1}{2}\sum_{i=1}^{n} \frac{\left(\eta_i - h_i(t_i, \boldsymbol{y}(t_i;\varrho), \varrho)\right)^2}{\sigma_i^2} \right\}.$$

$\Rightarrow$ Solved using `scipy.optimize.differential_evolution` routine in Python.

Fitting ODEs to data III

- Cost function: $C(\varrho) = C_1(\varrho) + C_2(\varrho)$, where

$$C_1(\varrho) = \sum_{i=1}^{n} \frac{(\eta_i^{(1)} - S(t_i, \varrho))^2}{\sigma_i^2}, \qquad C_2(\varrho) = \sum_{i=1}^{n} \frac{1}{\sigma_i^2} \left(\eta_i^{(2)} - N(0) - \nu \int_0^{t_i} P(s, \varrho) ds \right)^2$$

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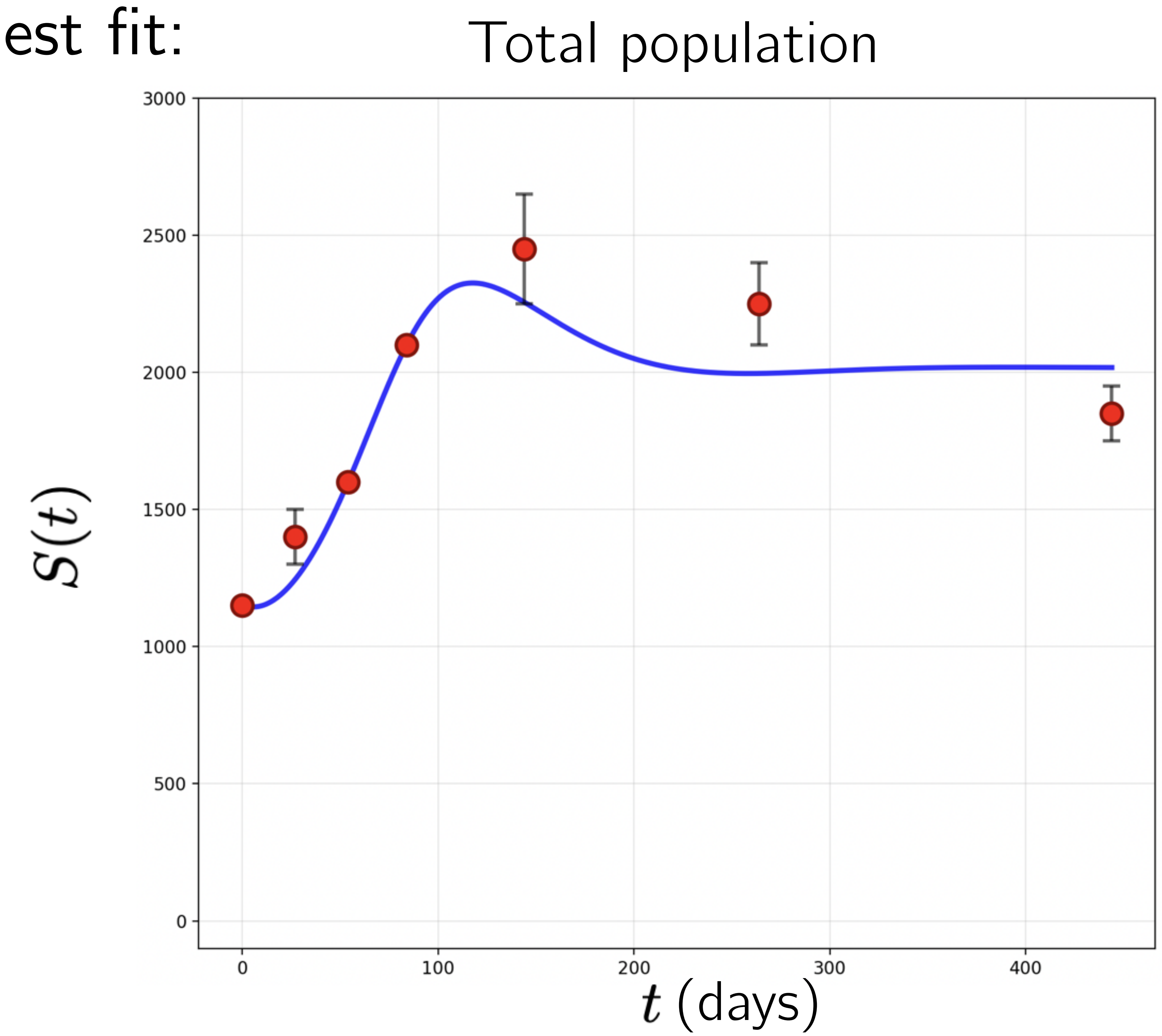
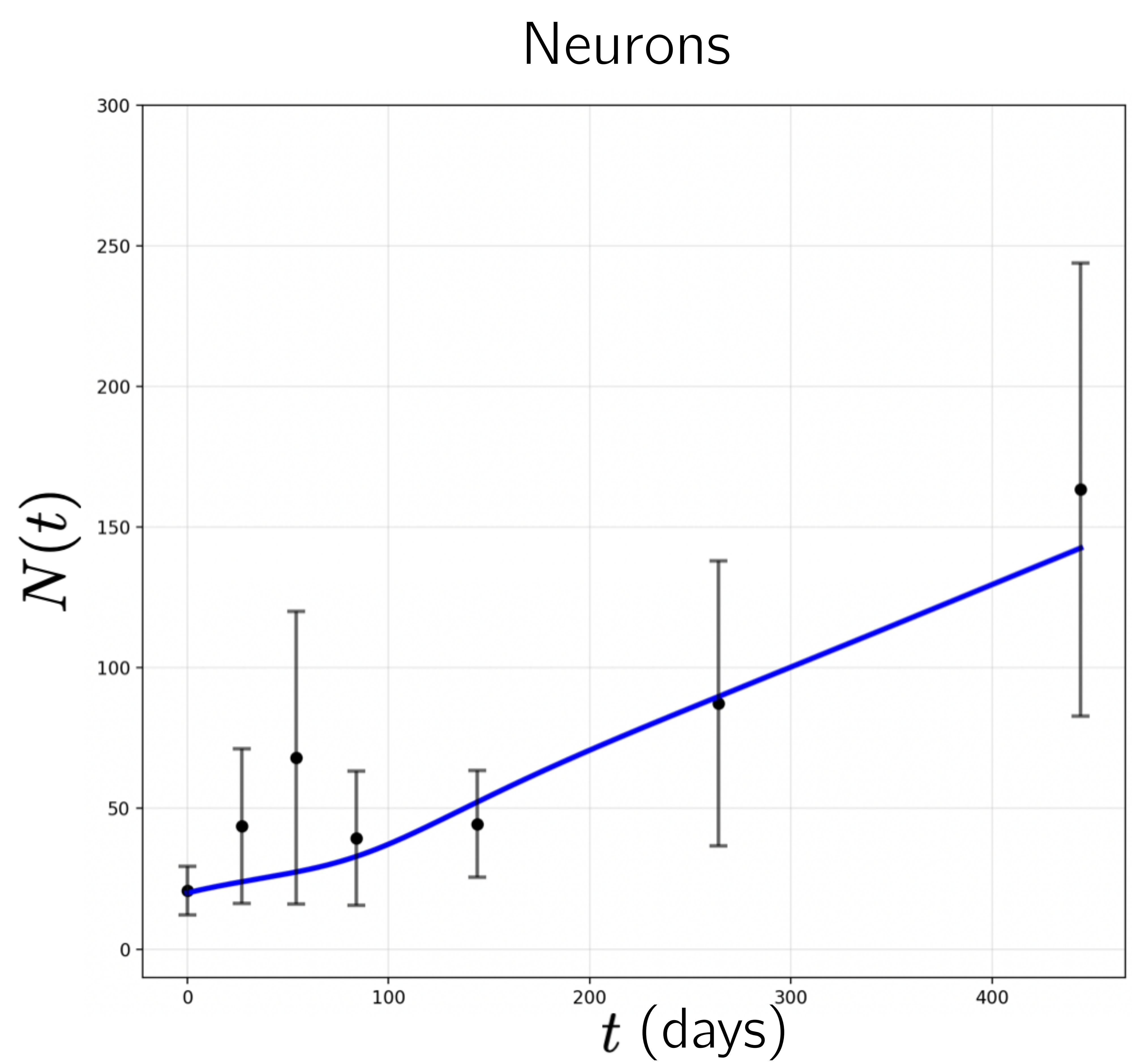
$$C_1(\varrho) = \sum_{i=1}^{n} \frac{(\eta_i^{(1)} - S(t_i,\varrho))^2}{\sigma_i^2}, \qquad C_2(\varrho) = \sum_{i=1}^{n} \frac{1}{\sigma_i^2}\left(\eta_i^{(2)} - N(0) - \nu \int_0^{t_i} P(s,\varrho)ds\right)^2$$

- Best fit:





Summary

- What has be done:
  1. We devised two ODE systems to model the evolution of Pallial NSC population in adult zebrafish from 3mpf to 4mpf and 4mpf to 20mpf respectively.
  2. We showed that the first system has a global solution and that its non-trivial steady state can be used to calibrate the second model
  3. We estimated parameters in the second model using two biological data sets and obtained satisfactory fits with it.

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- What to do next?
  1. Try with different choice of (x, y, z) to explore the effect of feedback on the fit
  2. Ask the biologists about the relevance of our perturbation and improve it if necessary.

Thank you!

questions?

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