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Supplementary information

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Three-dimensional mapping of intact ovaries reveals the aging dynamics of the ovarian reserve

In the format provided by the authors and unedited

Supplementary Note: Modelling Oocyte Dynamics

S1 Problem Overview

We observe counts of oocytes in four developmental stages across multiple ovaries and ages (weeks):

$$\text{Primordial (P)}, \quad \text{Primary (P2)}, \quad \text{Secondary (S)}, \quad \text{Antral (A)}.$$

For each ovary, we also have its organ volume. The goal is to model the dynamics of stage counts—including death and forward transitions—and to infer the underlying transition/death parameters together with standard errors.

S2 Data and Normalization

Let $y_{ik}(t)$ denote the observed count in stage $k \in \{0, 1, 2, 3\}$ for ovary i at week t, and let V_i be the ovary volume. To account for varying organ sizes, we analyze *densities* (counts per unit volume). This is implemented as:

$$\tilde{y}_{ik}(t) = \frac{y_{ik}(t)}{V_i/2}, \tag{1}$$

where the $1/2$ factor accounts for two ovaries per animal. After normalization, we stack all rows (ovaries $\times$ weeks) into a matrix $\mathbf{Y} \in \mathbb{R}^{n\times 4}$.

S3 Mechanistic Model: Compartments, Flows, and Death

We adopt a linear compartmental model with four states $\boldsymbol{N}(t) = (N_0(t), N_1(t), N_2(t), N_3(t))^\top$ representing the latent stage densities. The dynamics are governed by:

- **Forward transitions** from stage j to $j+1$ with rate p_j.
- **Death** within each stage j with rate d_j.

The dynamics follow the linear system of ordinary differential equations (ODEs):

$$\frac{d}{dt}N_0 = -(d_1 + p_1)\, N_0, \tag{2}$$

$$\frac{d}{dt}N_1 = p_1 N_0 - (d_2 + p_2)\, N_1, \tag{3}$$

$$\frac{d}{dt}N_2 = p_2 N_1 - (d_3 + p_3)\, N_2, \tag{4}$$

$$\frac{d}{dt}N_3 = p_3 N_2 - d_4 N_3. \tag{5}$$

In matrix form, $\dot{\boldsymbol{N}}(t) = \mathbf{A}\,\boldsymbol{N}(t)$ with:

$$\mathbf{A} = \begin{bmatrix} -(d_1+p_1) & 0 & 0 & 0 \\ p_1 & -(d_2+p_2) & 0 & 0 \\ 0 & p_2 & -(d_3+p_3) & 0 \\ 0 & 0 & p_3 & -d_4 \end{bmatrix}.$$

Throughout the main analysis, we fix $d_2 = d_3 = 0$ based on biological considerations and identifiability. The free parameters are $\boldsymbol{\theta} = (p_1, p_2, p_3, d_1, d_4)^\top$.

S4 Initial Conditions and Numerical Solution

For each ovary observed at week 5, we have a complete 4-vector of stage densities. We define the fitting initial condition as the mean across week-5 replicates:

$$\boldsymbol{N}_{\text{mean}}(5) = \frac{1}{|\mathcal{I}_5|} \sum_{r \in \mathcal{I}_5} \mathbf{Y}(r, \cdot).$$

Because the system is linear with constant coefficients, we compute $\boldsymbol{N}(t)$ using a robust ODE integrator (`solve_ivp`, RK45).

S5 Parameter Estimation via Nonlinear Least Squares

We treat the observations as noisy measurements: $\tilde{y}_{ik}(t_r) = N_k(t_r; \boldsymbol{\theta}) + \varepsilon_{ik}(t_r)$, where $\varepsilon_{ik}(t_r) \sim \mathcal{N}(0, \sigma_k^2)$. To improve numerical conditioning, we scale residuals by an empirical per-stage factor s_k:

$$r_{ik}(t_r; \boldsymbol{\theta}) = \frac{\tilde{y}_{ik}(t_r) - N_k(t_r; \boldsymbol{\theta})}{s_k}.$$

We estimate $\boldsymbol{\theta}$ by minimizing the sum of squared scaled residuals subject to bounds:

$$\widehat{\boldsymbol{\theta}} = \arg\min_{\boldsymbol{\theta} \in [\text{LB}, \text{UB}]} \|\boldsymbol{r}(\boldsymbol{\theta})\|_2^2.$$

Standard errors are derived from the Jacobian $\mathbf{J}(\widehat{\boldsymbol{\theta}})$ using the Gauss–Newton approximation: $\widehat{\text{Cov}}(\widehat{\boldsymbol{\theta}}) \approx \widehat{s}^2\,(\mathbf{J}^\top \mathbf{J})^\dagger$, where $\widehat{s}^2 = \text{RSS}/(m-p)$.

S6 Identifiability and Constraints

Even with all four series observed, some parameters are weakly identified. Trade-offs between death rates and preceding transition rates can yield similar flows. Fixing $d_2 = d_3 = 0$ alleviates this instability, particularly when secondary and antral counts are small and noisy.

S7 Results

The estimated parameters and associated uncertainties are provided in Figure 4.