Feedback control of organ size precision in the *Drosophila* eye

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Biological processes are intrinsically noisy and yet, the result of development like the species-specific size and shape of organs is usually remarkably precise. This precision suggests the existence of mechanisms of feedback control that ensure that deviations from a target size are minimized. Still, we have very limited understanding of how these mechanisms operate. Here, we investigate the problem of organ size precision using the *Drosophila* eye. The size of the adult eye depends on the rates at which eye progenitor cells grow and differentiate. We first find that the progenitor net growth rate results from the balance between their proliferation and apoptosis, with this latter contributing to determining both final eye size and its variability. In turn, apoptosis of progenitor cells is hampered by Dpp, a BMP2/4 signaling molecule transiently produced by early differentiating retinal cells.

Our genetic experiments show how the status of retinal differentiation is communicated to progenitors through the differentiation-dependent production of Dpp which, by adjusting the rate of apoptosis, exerts a feedback control over the net growth of progenitors to reduce final eye size variability.

To dissect the dynamics of eye growth and differentiation, we have devised a theoretical model that captures the essential biological processes involved. This model is defined by three key variables: the width of the progenitor cell region (G), the width of the differentiated retinal cell region (R), and an intermediary strip of recently differentiated retinal cells (R_n) that produce Dpp. These variables collectively encapsulate the transformative stages of cellular development in the eye.

The dynamics of these variables are governed by the interplay of progenitor cell proliferation, apoptosis, and cellular differentiation, with transitions from progenitor cells to newly differentiated cells ($G \rightarrow R_n$) and from newly differentiated to fully differentiated retinal cells ($R_n \rightarrow R$). To account for the intrinsic stochasticity in biological systems, we have incorporated this interplay into a set of three Langevin equations. These equations, with noise terms modeling the fluctuations related to each of the basic processes in play, effectively capture the fluctuations inherent in the biological processes.

Our model faithfully reproduces the observed dynamics of eye growth and differentiation in experimental settings. Moreover, it provides a means to investigate the contribution of each process's fluctuations to the asymmetry typically seen between the two eyes of a single fly. Through linear stability analysis, we further demonstrate the stabilizing role of apoptosis in arresting eye growth. Consequently, our model not only captures the dynamics of eye development but also provides a framework for exploring the complex interplay of the constituent processes and their roles in developmental robustness.

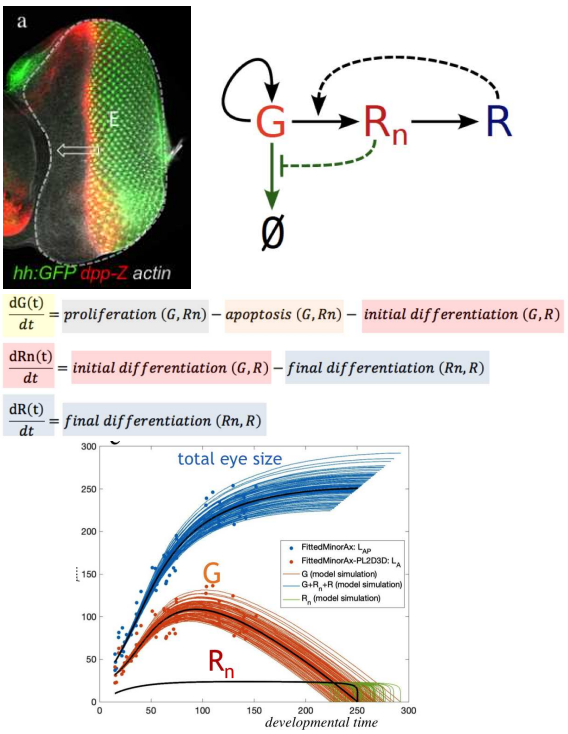

Fig. 1. The eye primordium of the developing fly embryo showing dividing progenitor cells (G) cells to the left and differentiated retinal cells (R) to the right; in between a narrow strip of newly differentiated retinal cells (R_n) produce Dpp. Dpp produced by newly differentiated cells inhibits apoptosis of progenitors, *hedgehog* produced in retinal cells activates differentiation. These processes are modeled through a set of differential equations, when including stochastic terms, they reproduce the dynamics and variability of eye development.

[1] T. Navarro, A. Iannini, M. Neto, A. Campoy-Lopez, J. Muñoz-García, S. Ares, and F. Casares, *Feedback control of organ size precision is mediated by BMP2-regulated apoptosis in the Drosophila eye*, submitted to PLoS Biology, second round of review (2023).