QUANTITATIVE DEVELOPMENTAL BIOLOGY

Jeroen van Zon

Our central question is how cells in developing organisms make decisions and self-organize into intricate patterns, despite strong variability on the molecular and cellular level. We use two simple biological model systems, the nematode worm *C. elegans* and intestinal organoids, the latter in collaboration with the group of Sander Tans. We study these by custom microscopy, quantitative image and data analysis and predictive mathematical modeling, often in collaboration with biologists studying similar questions by genetic approaches.

Highlights

- Combining biophysics measurements and stochastic simulations, we identified a novel mechanism that prevents spontaneous reversals of a cell fate switch in *C. elegans*, explaining why neuronal fate is never lost during the animal's life.
- Using our unique ability to follow cell dynamics throughout development in moving worms, we demonstrated that cell division and gene expression timing adjusts precisely to environmentally-induced slowdown of development.
- We development a cutting-edge image analysis pipeline, based on deep learning neural networks, that enables fully automated tracking of all cells in intestinal organoids, and used this pipeline to study control of proliferation and differentiation.

Plans

For worms, an emerging direction is control of body growth and developmental timing, and how this depends on external stresses that slowdown or arrest development. Here, we build on our exciting discovery that insulin signaling controls growth and arrest through pulses that are stochastic, yet synchronized throughout the body. For organoids, we will expand to systems such as lung and liver, and address medically-relevant questions, including proliferation patterns in cancer and interactions between organoids and immune cells. We will further push our neural network approaches, to predict organoid cell types or features such as cell volume in a label-free manner.

Key research items

1. J.J.H. Traets, S.N. van der Burght, G. Jansen and J.S. van Zon, *Mechanism of life-long maintenance of neuron identity despite molecular fluctuations*, Elife, 10:e66955 (2021)
2. O. Filina, B. Demirbas, R. Haagmans and J.S. van Zon, *Temporal scaling in C. elegans larval development*. PNAS 119:e2123110119 (2022)
3. https://github.com/jvzonlab/OrganoidTracker. *Software for our organoid cell tracking approach*, described in Kok et al, PLoS One (2020)
4. G. Huelsz-Prince, R.N.U. Kok, Y.J. Goos, L. Bruens, X. Zheng, S.I. Ellenbroek, J. van Rheenen, S.J. Tans and J.S. van Zon, *Mother cells control daughter cell proliferation in intestinal organoids to minimize proliferation fluctuations*, Elife, 11:e80682 (2022)
5. M. Betje, X. Zheng, R.N.U. Kok, J.S. van Zon and S.J. Tans, Cell Tracking for Organoids: *Lessons From Developmental Biology*, Front. Cell. Dev. Biol., 9:675013 (2021) [Invited review]

Single molecule imaging in a *C. elegans* worm to quantify gene expression (top) and cell tracking in organoids to measure cell lineages (bottom).