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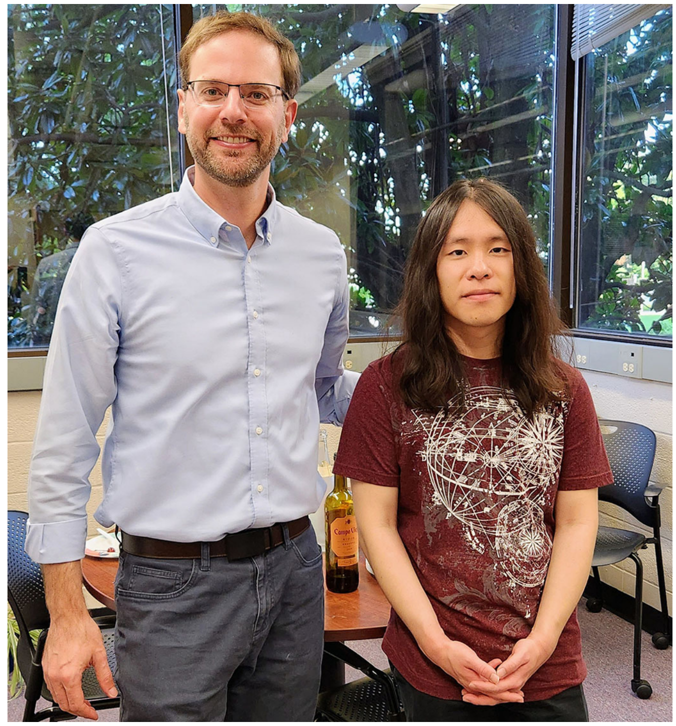
INTERVIEW

The people behind the papers – Jason Ko and Daniel Lobo

Planarians grow when they are fed and shrink during periods of starvation. However, it is unclear how they maintain appropriate body proportions as their size changes. A new paper in Development investigates the differences between growth and shrinkage dynamics and builds a mathematical model to explore the mechanisms underpinning these two processes. To learn more about the story behind the paper, we caught up with first author, Jason Ko, and corresponding author, Daniel Lobo, Associate Professor at the University of Maryland.



Daniel Lobo (left) and Jason Ko (right)

Daniel, can you give us your scientific biography and the questions your lab is trying to answer?

DL: My lab seeks to understand the biological mechanisms controlling growth, shape and form. I was trained in both computational and molecular techniques, which now I integrate in a comprehensive systems biology approach in the context of developmental, cancer and synthetic biology. We advance the field with new computational and molecular methods that we then use to extract mechanistic understanding from complex and dynamic phenotypes.

Jason, how did you come to work in the lab and what drives your research today?

JK: I originally went to university to study video game programming, but eventually realised I was more interested in understanding how rules lead to complex spatial dynamics. This led me to join a group of undergraduates working with the late Dr Harold Morowitz to investigate the trait of eutely (cell constancy) in the roundworm *Caenorhabditis elegans*. Although Dr Morowitz was a great mentor who inspired me to consider how having a worm inside the computer might help us better understand novel developmental traits, he did not have the computational skills to give me specific guidance. When I discovered Dr Lobo's work on computational models to understand regeneration in planarian flatworms, and noticed he was looking for PhD students, I saw a great opportunity. This interest in understanding the fundamental rules by which shape and form are regulated continues to motivate me.

Can you tell us about the background of the field that inspired your work?

DL & JK: Planarians are famous for their regenerative capabilities, being able to regenerate any lost body part after amputation, including complex organs such as the eye or brain. Further, they can grow when fed but shrink when starved, maintaining precise proportions. Although this trait has been studied since the 1890s, the mechanisms behind it are still not fully understood. The advent of molecular biology techniques has significantly advanced our understanding of how morphological form is created and maintained, but no comprehensive model currently exists to explain the mechanisms controlling planarian shape plasticity. Mathematical and computational methods can provide mechanistic insights into complex phenotypes, including the interactions between genetic signals and tissue growth. We combined this approach with precise experimental data and image analysis to understand the dynamic feedback between morphogen signals and whole-body shapes in planarians.

> Mathematical and computational methods can provide mechanistic insights into complex phenotypes, including the interactions between genetic signals and tissue growth

Can you give us the key results of the paper in a paragraph?

DL & JK: Through imaging and analysis of planarian body shapes and development of a descriptive model, we demonstrate that planarians have different body proportions during growth and degrowth. We then developed a mechanistic model whereby a dynamic feedback loop between morphogen signals and tissue shapes can produce a worm-like shape. In order to parameterise this model, we developed an evolutionary algorithm approach that minimises the difference in shapes between the descriptive and mechanistic models. This model demonstrates that differential growth at the poles and apoptosis can explain growth and degrowth dynamics. These results will pave the way to identifying

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The extraordinary plasticity of planarian body shapes. When fed, planarians can grow from a small (left) to a large (right) correctly proportioned body within 9 weeks, a process that is reversed when starved.

the exact genes and signals that may implement such a mechanism *in vivo*.

When doing the research, did you have any particular result or eureka moment that has stuck with you?

JK: One of the main challenges with this project is that a single model can take 2 hours or more to execute, and we must simulate many models in the process of evolving good parameters. Realising that I could define fitness in such a way that simulations could be terminated early was a big deal because it meant we could run more simulations in a reasonable time frame. I think this was a major reason why our approach remains tractable.

And what about the flipside: any moments of frustration or despair?

JK: Although we use an evolutionary algorithm to find model parameters 'automatically', this process requires significant research effort. Namely, we need to create a metric that will quantitatively separate good shapes from bad shapes. It was very frustrating that prior versions of the algorithm could result in shapes that were highly distorted, such as hourglasses, or diamonds, but with very low error scores. From a human perspective, it's easy to say, 'No, that obviously doesn't look anything like a planarian!' But, of course, the machine doesn't share our human visual intuition. Ultimately, this frustration strikes at the heart of programming – humans must continuously learn how to translate what we understand intuitively into a procedure that machines can follow.

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Why did you choose to submit this paper to Development?

DL & JK: We think the combination of experimental data and computational techniques applied to a fundamental problem in developmental biology such as how biological forms are regulated would be of great interest to the readers of Development.

Jason, what is next for you after this paper?

JK: I recently finished my PhD at UMBC and I am currently looking for post-doc opportunities in research to further investigate the relationship between rules and spatial dynamics. I am also considering positions outside of biology. This is partially because I want to incorporate some of the focus on tools that I lost in my transition from games to biology, and partially because I am interested in ways to make models such as the one we present in our paper execute faster. Perhaps in the future, biological models like this one will execute in seconds, rather than hours.

Daniel, where will this story take your lab next?

DL: These results are giving us insights into the fundamental mechanisms that control shape and form. We are seeking to further validate the model by identifying the genes and signals that implement the discovered mechanism by performing loss-of-function assays with candidate genes that will test and refine the model. In addition, we are interested in understanding how planarians pattern and scale their body parts during growth and degrowth and how these signals are integrated with those controlling body proportions. Towards this, we are also developing new mathematical and computational modelling to be able to track stem cell differentiation and migration and the signals precisely orchestrating these cellular behaviours that together result in the correct planarian body.

Reference

Ko, J. M., Reginato, W., Wolff, A. and Lobo, D. (2024). Mechanistic regulation of planarian shape during growth and degrowth. *Development* **151**, dev202353. doi:10.1242/dev.202353