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INTERVIEW

The people behind the papers – Megan Rommelfanger and Adam MacLean

Cell fate decisions are dependent on both internal and external factors, but mathematical models of this process have often neglected the external signals. A new paper in Development describes a multiscale model that integrates intracellular gene regulatory networks with a cell-cell communication network at single-cell resolution. We caught up with the authors, PhD student Megan Rommelfanger and Adam MacLean, Assistant Professor at the University of Southern California, to find out more about their research.

Megan (L) and Adam (R)

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

AM: I took my first biology class (biophysics) in the final semester of an undergraduate degree in theoretical physics, and I never looked back. I completed a PhD in systems biology at Imperial College London with Michael Stumpf, followed by a postdoc at Oxford with Heather Harrington and Helen Byrne. During my research over this time, I became fascinated by stem cell dynamics and cell fate decisions, which I studied using dynamical systems modelling and inference. Then, as I moved for a postdoc position to the University of California Irvine with Qing Nie, a relatively new technique called single-cell RNA-sequencing was becoming rather popular. Excited by the potential of these technologies to reveal stem cell states and, crucially, the dynamic transitions between them, I dived in and began to develop methods for the analysis of single-cell genomics data. The biggest contribution I made during my postdoc was developing the first computational method to predict cell-cell communication networks at the resolution of single cells.

I started a lab at the University of Southern California (USC) in 2019. The questions we seek to answer regard cell fate decision-making in adult stem cells and developmental lineages. I have a long-standing interest in haematopoiesis, but also study cell fate decision-making in the developing kidney (nephrogenesis) and its dysregulation in epithelial cancers. We are a fully computational lab, focused on the development of new mathematical methods and models sufficient to gain new insight into these systems. The tools we use draw from dynamical systems theory, statistical inference and machine learning.

Megan, how did you come to work in Adam's lab and what drives your research today?

MR: My training before graduate school was in maths, and I wanted to work in a lab where I would be able to implement a diverse array of mathematical tools to tackle biological problems. In Adam's lab, I've had the opportunity to use techniques ranging from dynamical systems to information theory to study hematopoietic cell lineage commitment. Working with Adam, I've also been able to learn how the biology informs the methods we use. It has been a fantastic experience working with different experimental collaborators and seeing how we can use various computational approaches to provide them with useful analysis!

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I am fascinated by how hematopoietic stem cells produce and maintain all the different types of specialised blood cells in the body. They are also able to respond to environmental cues to increase or decrease production of different cell types, depending on what is required in that moment. On an individual cell level, lineage specification depends on cell-internal dynamics such as gene regulatory networks or stochasticity of gene expression, and cell-extrinsic dynamics such as cell-cell signalling or environmental conditions. Each of these factors are individually complex, so understanding how they all work together to achieve specific population-level behaviours is challenging!

Before your work, what was known about cell fate specification of myeloid progenitors?

AM: For years a canonical model existed: stochastic cell fate choice controlled by the mutual inhibition of the transcription factors GATA1 and PU.1. Five years ago, using elegant live imaging experiments, Hoppe et al. (2016) showed that random fluctuations in protein ratios alone were not sufficient to induce bipotent cell fate commitment to the granulocyte-monocyte or the erythroid-megakaryocyte lineages. The missing 'push', or external signal,

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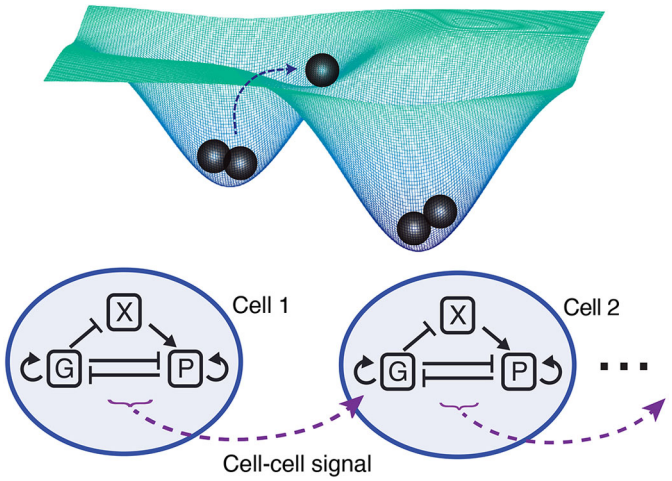

Top: The simple two-attractor state model. Bottom: Schematic of the multiscale model incorporating both the intracellular gene regulatory network and the external signal module.

could have come from cell-cell communication or many other sources. To rigorously test how cell-cell communication impacts cell fate choices in the canonical models, we needed a new theoretical framework. The result of that is this paper.

How does your model differ from previous efforts to model lineage specification?

MR: The vast majority of models of lineage specification neglect cell-cell signalling, despite cell-cell signalling being widely acknowledged as playing a pronounced role in cell lineage commitment. The few existing models that do incorporate cell-cell signalling make simplifying assumptions with respect to either the internal cell dynamics or the extracellular signalling. Our model is different in that we model both the cell-internal gene regulatory network dynamics and the cell-external signalling with appropriate levels of resolution. We model the cell-internal gene regulatory networks using ordinary differential equations (ODEs). Then, we treat cell-cell signalling as a Poisson process, in which the signals received by a cell influence its internal dynamics by altering the parameters of the ODE system.

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

AM: No cell is an island. Incorporating communication between cells into models of cell fate as dictated by the GATA1-PU.1 gene regulatory network led to profound shifts in the distributions of cell fates. Furthermore, in studying the cumulative effects of signalling, hallmarks of cooperativity emerged. Signals propagating down chains of communicating cells acted to reinforce the cell fate decision being made. This held true across a broad range of topologies including feedback and feedforward loops, as well as in the presence of noise. Strikingly, the addition of noise to the cell signalling changed not only the variance of the cell fate distributions but also the mean, i.e. noise itself altered cell fate decision-making boundaries. This was true for both extrinsic and intrinsic noise, although, in agreement with recent literature, we showed that extrinsic noise was the more important of the two and the dominant source. Finally, we showed that spatially restricted patterns of communicating cells led to different cell fate distributions than did populations of well-mixed cells. Although at the limits of what can be currently tested in the lab, this is rapidly changing and spatial transcriptomics coupled with other data modalities will soon allow us to test these predictions *in vivo*.

No cell is an island

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

MR: I don't remember any specific eureka moments! Constructing the model was primarily a process of tweaking, testing and repeating until we landed upon a model that made mathematical and biological sense.

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

MR: Simulations rarely output perfect results on the first try when there are many parameters to adjust, so there were often moments of frustration from redoing simulations over and over!

Megan, what's next for you after this paper?

MR: Next, I'm really excited about working on modelling with single-cell multiomic data (sequencing RNA and ATAC from the same single cells). This new data type gives us a more dynamic view of the state of each individual cell, thus enabling us to better fit models to our data. By giving us a deeper understanding of the epigenetic changes throughout development at the resolution of single cells, single-cell multiomic data has the potential to significantly advance our understanding of hematopoietic cell fate specification.

Where will this story take the MacLean lab?

AM: We are only just beginning to understand how cell-cell communication shapes cell fate decision-making. There is so much more to do! We will continue to study haematopoiesis through the development of more detailed models. Data can help to constrain these models, for example by obtaining specific cell signalling topologies via spatial transcriptomics, or linking transcriptional states to fates via clonal barcoding and lineage tracing. We are also developing methods to study core gene regulatory networks that control other cell fate decision points; new networks that can be fed into future cell-cell communication models.

Finally, let's move outside the lab – what do you like to do in your spare time?

MR: In southern California we are near many beautiful beaches, so I try to go as often as I can – Manhattan Beach is my favourite! I also enjoy yoga, running, and watching college basketball.

AM: Parenting small children, albeit delightful, makes spare time vanishingly sparse. When opportunities do arise, I like to head out of the city into the deserts and mountains of California to walk, camp and ski.

References

Rommelfanger, M. K. and MacLean, A. L. (2021). A single-cell resolved cell-cell communication model explains lineage commitment in hematopoiesis. *Development* **148**, dev199779. doi:10.1242/dev.199779

Hoppe, P. S., Schwarzfischer, M., Loeffler, D., Kokkaliaris, K. D., Hilsenbeck, O., Moritz, N., Endele, M., Filipczyk, A., Gambardella, A., Ahmed, N. et al. (2016). Early myeloid lineage choice is not initiated by random PU.1 to GATA1 protein ratios. *Nature* **535**, 299-302. doi:10.1038/nature18320