BIRS, May 5th, 2022

Mechanistic modelling of cell migration in the immune system

"Transparent modelling" beyond ML

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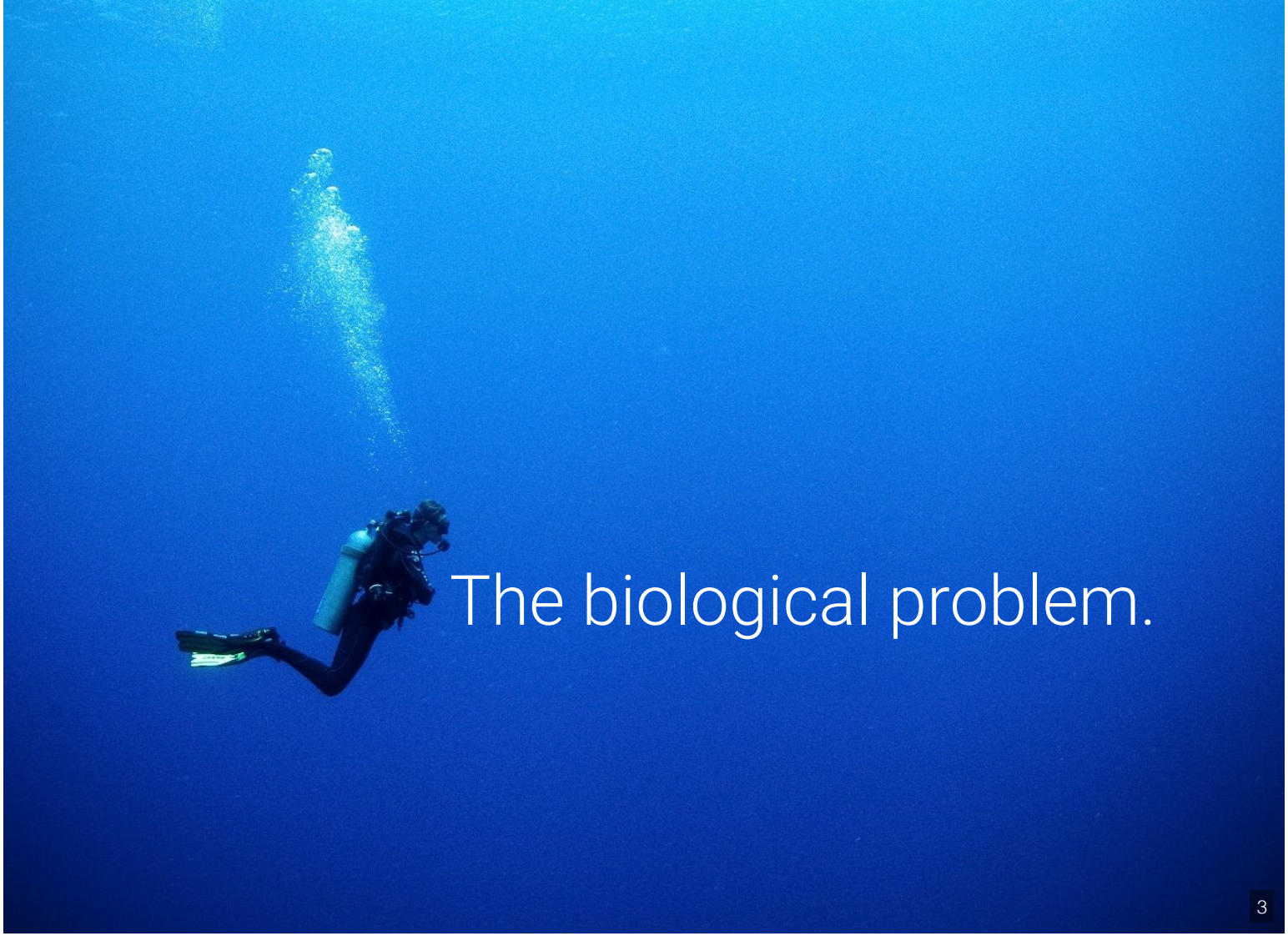
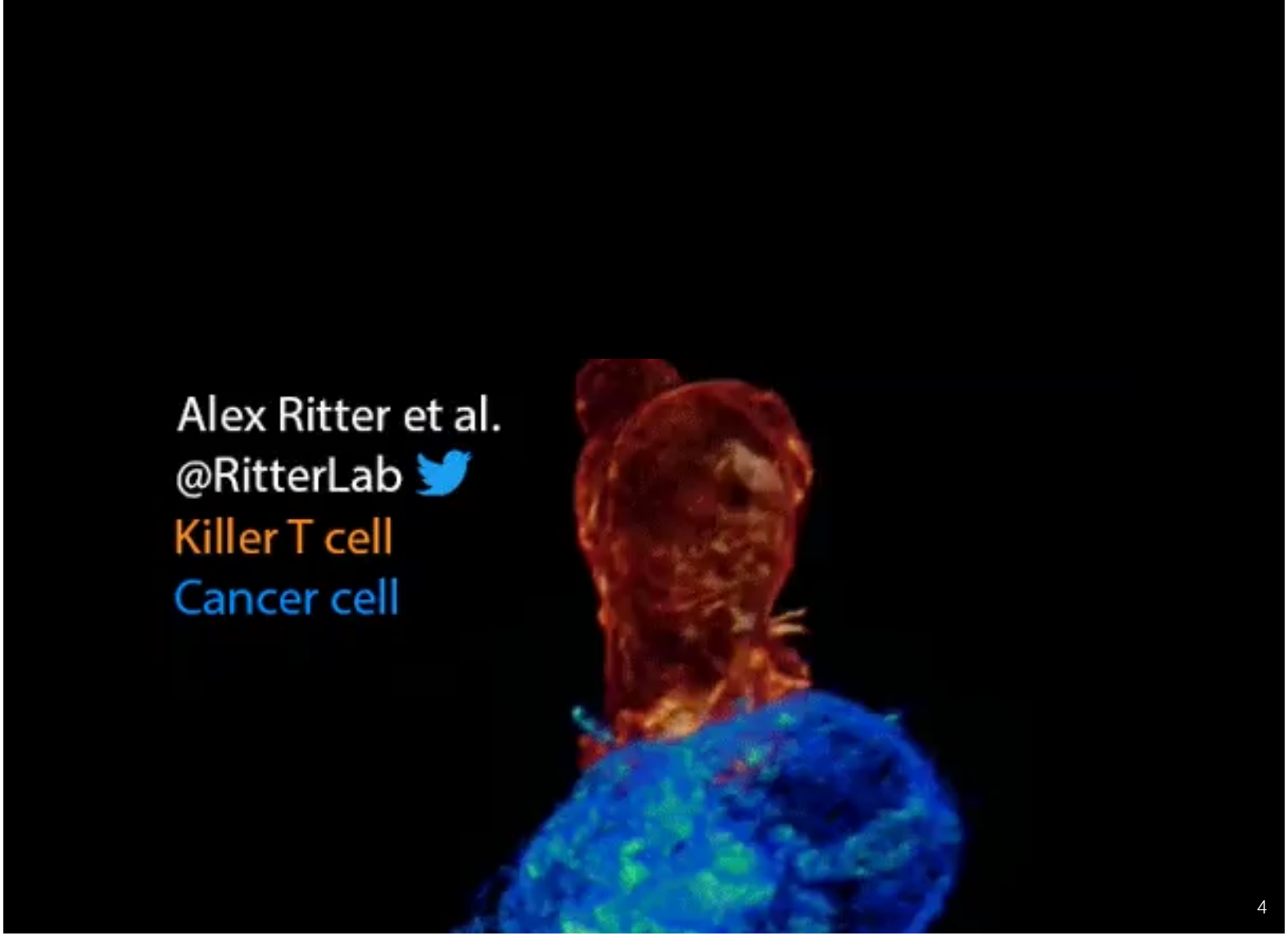
Please view this presentation at https://computational-immunology.org/inge/presentations/banff for the best experience.

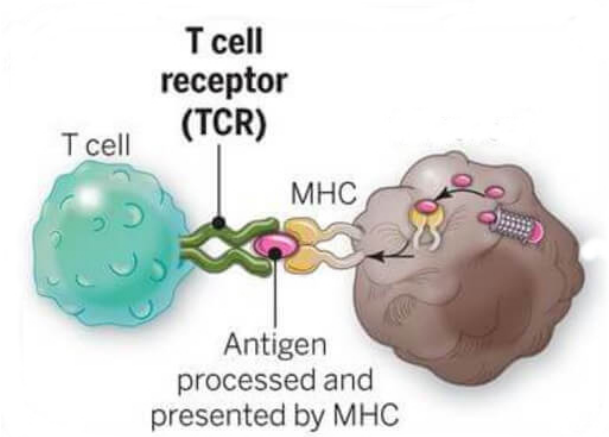

The biological problem.


Alex Ritter et al.
@RitterLab
Killer T cell
Cancer cell

T cells as anomaly detectors.

T cells:

- Detect and clean up infected/cancerous cells

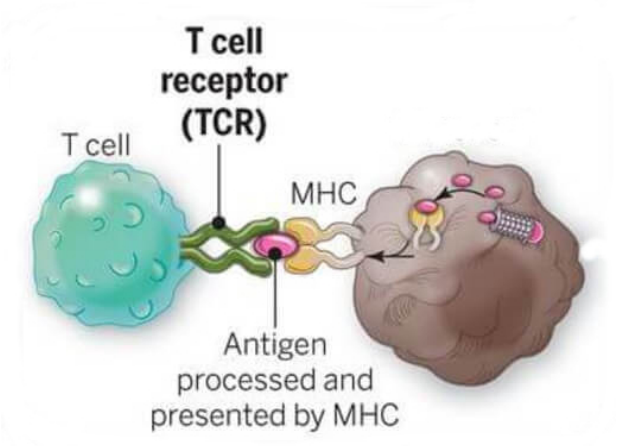


Adapted from National Cancer Institute (NIH)

T cells as anomaly detectors.

T cells:

- Detect and clean up infected/cancerous cells
- Using their T-cell receptor (TCR) to screen for short peptides displayed on a molecule called MHC



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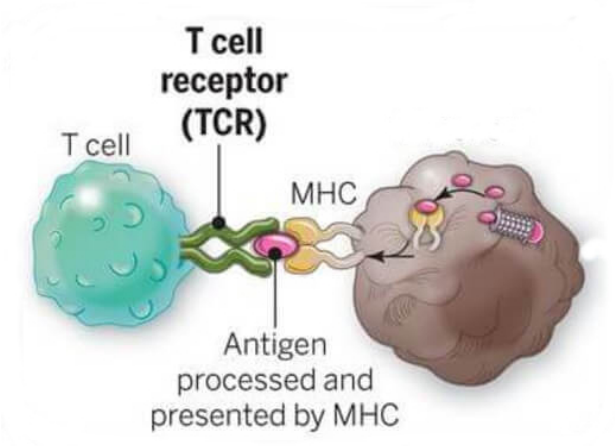

T cells as highly specialized anomaly detectors.

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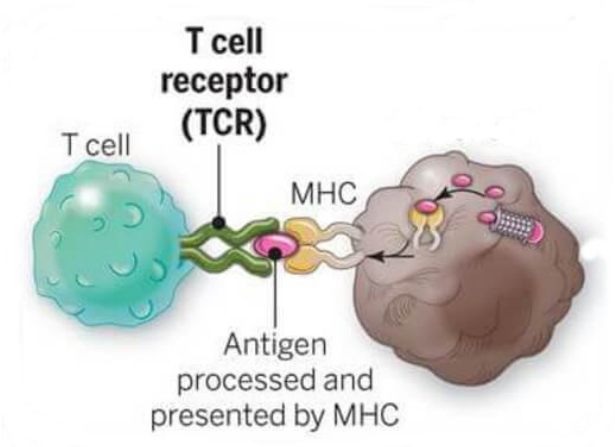
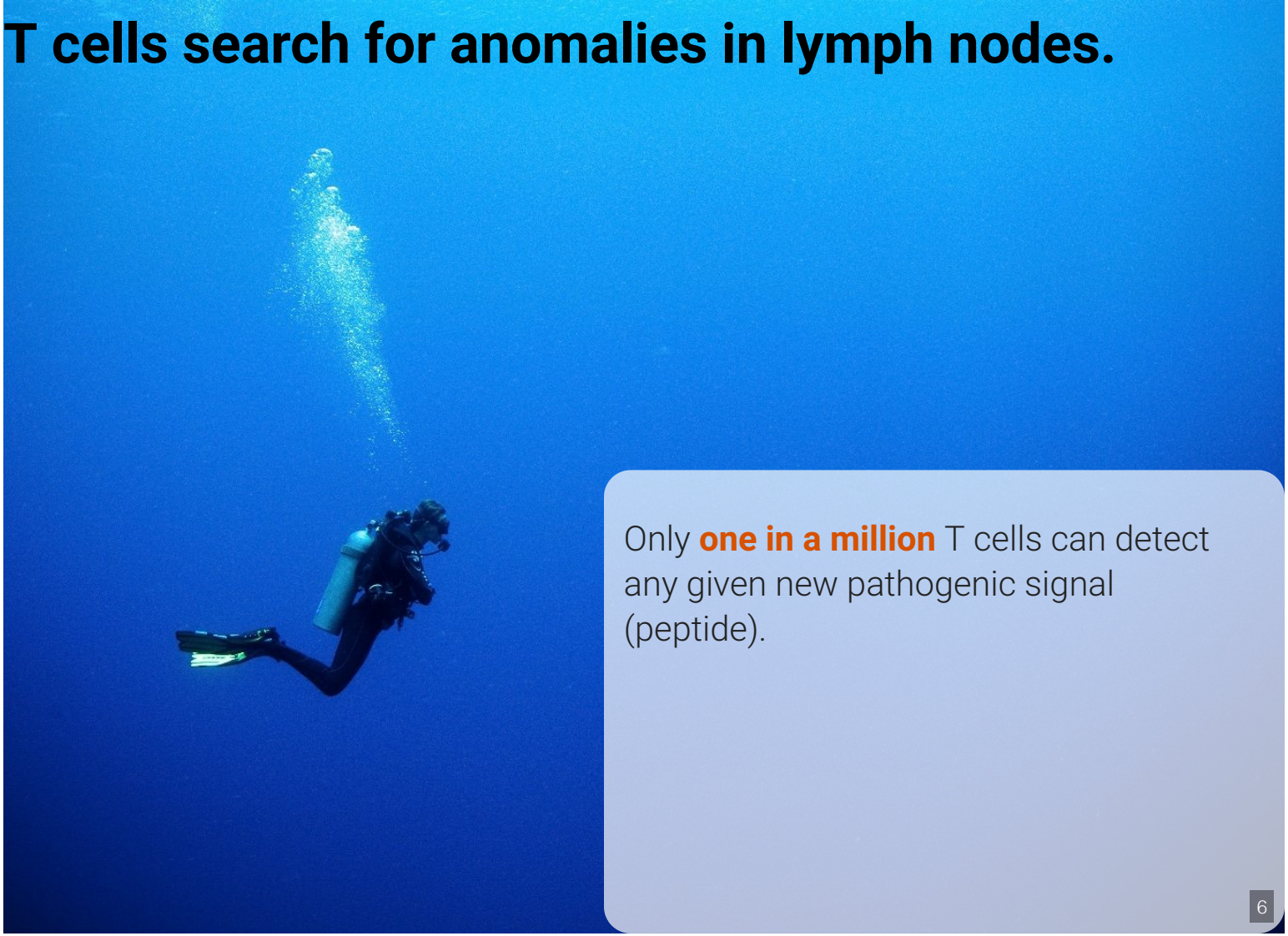
- Using their T-cell receptor (TCR) to screen for short peptides displayed on a molecule called MHC
- Compromised (infected/cancerous) cells display different peptides than healthy cells do
  → "anomaly detection"
- Specific because each T cell's receptor recognises specific peptides



T cells search for anomalies in lymph nodes.



Only **one in a million** T cells can detect any given new pathogenic signal (peptide).

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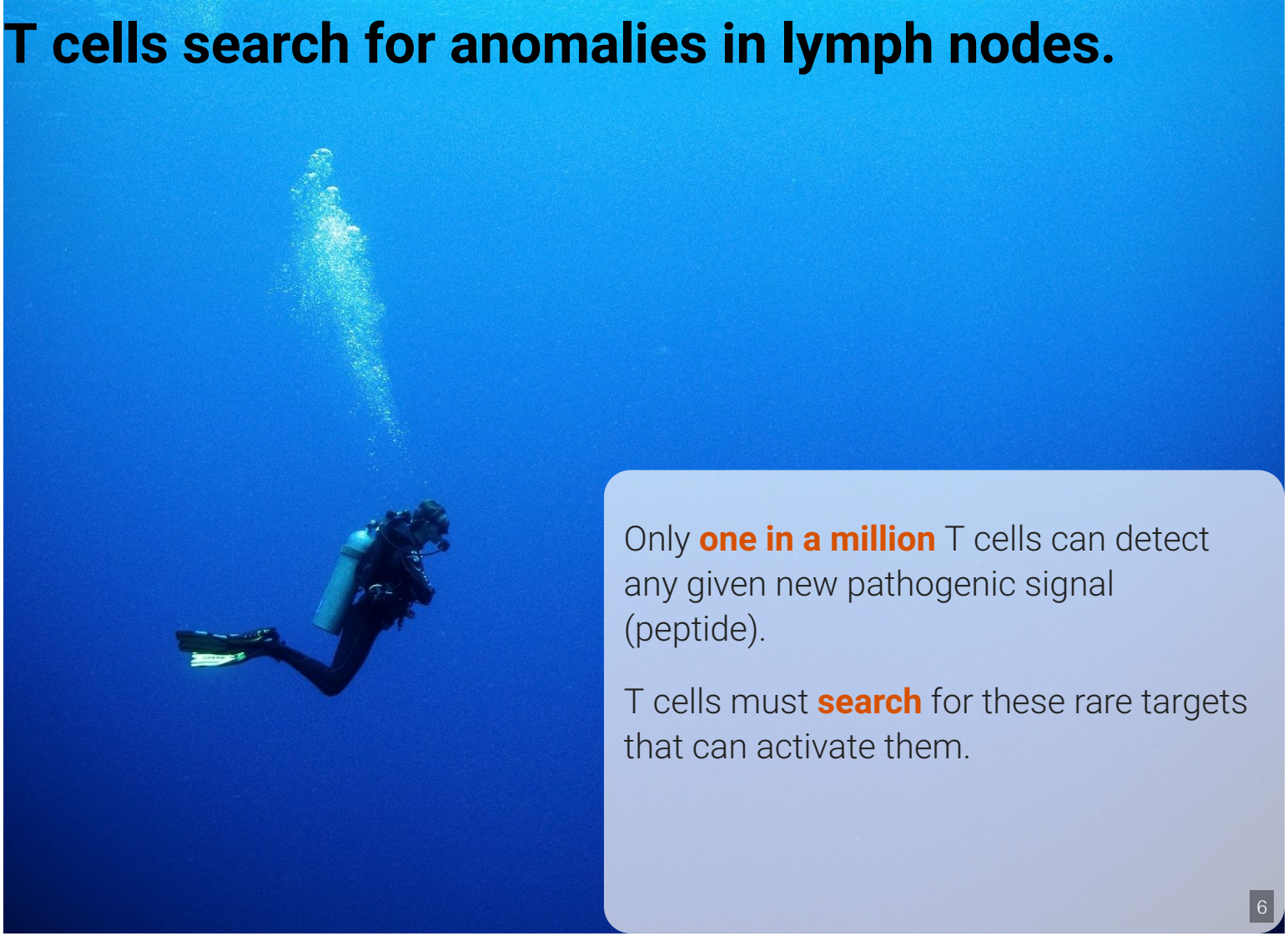

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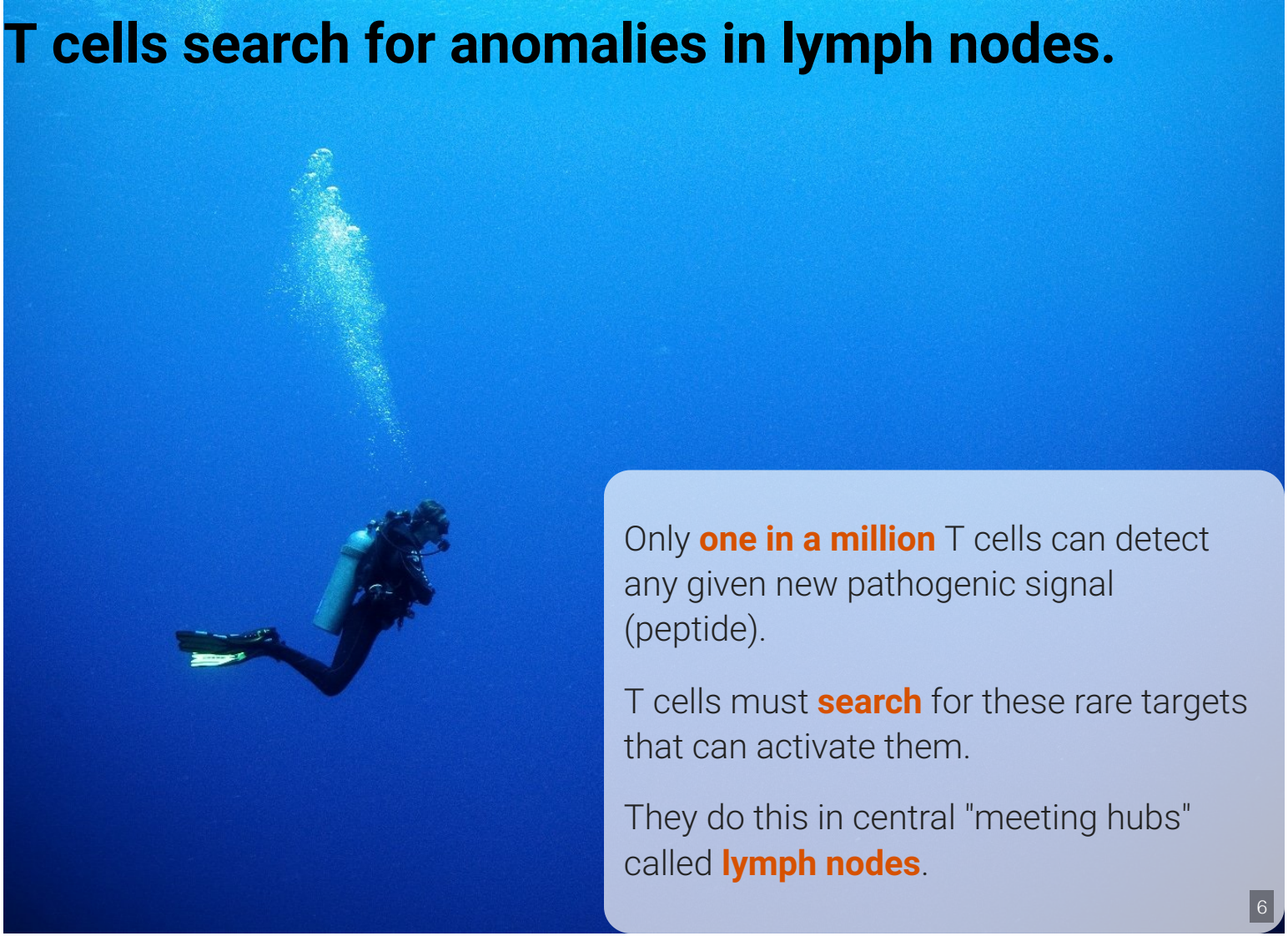

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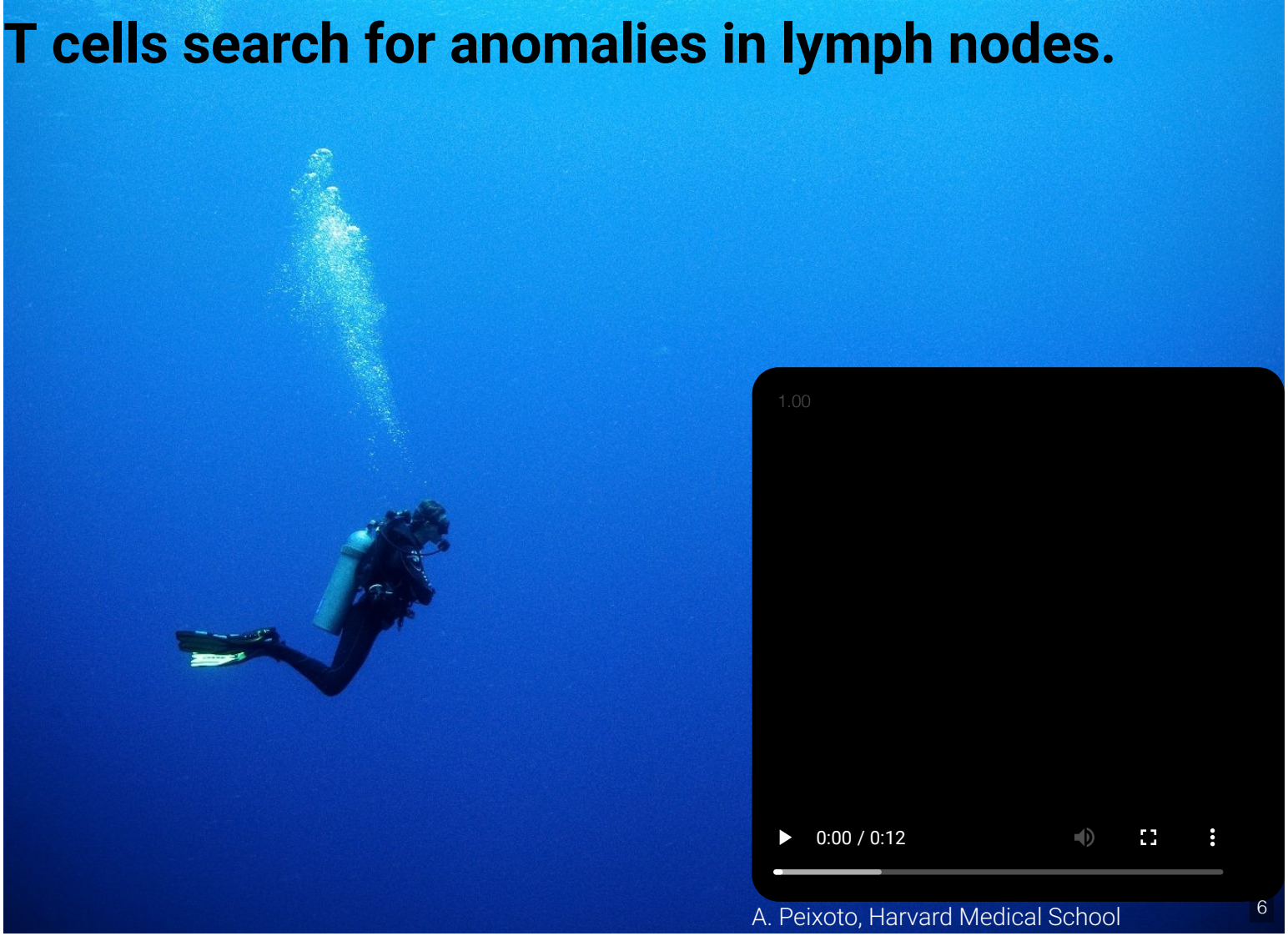
They do this in central "meeting hubs" called **lymph nodes**.

T cells search for anomalies in lymph nodes.



A. Peixoto, Harvard Medical School

Hidden figures.

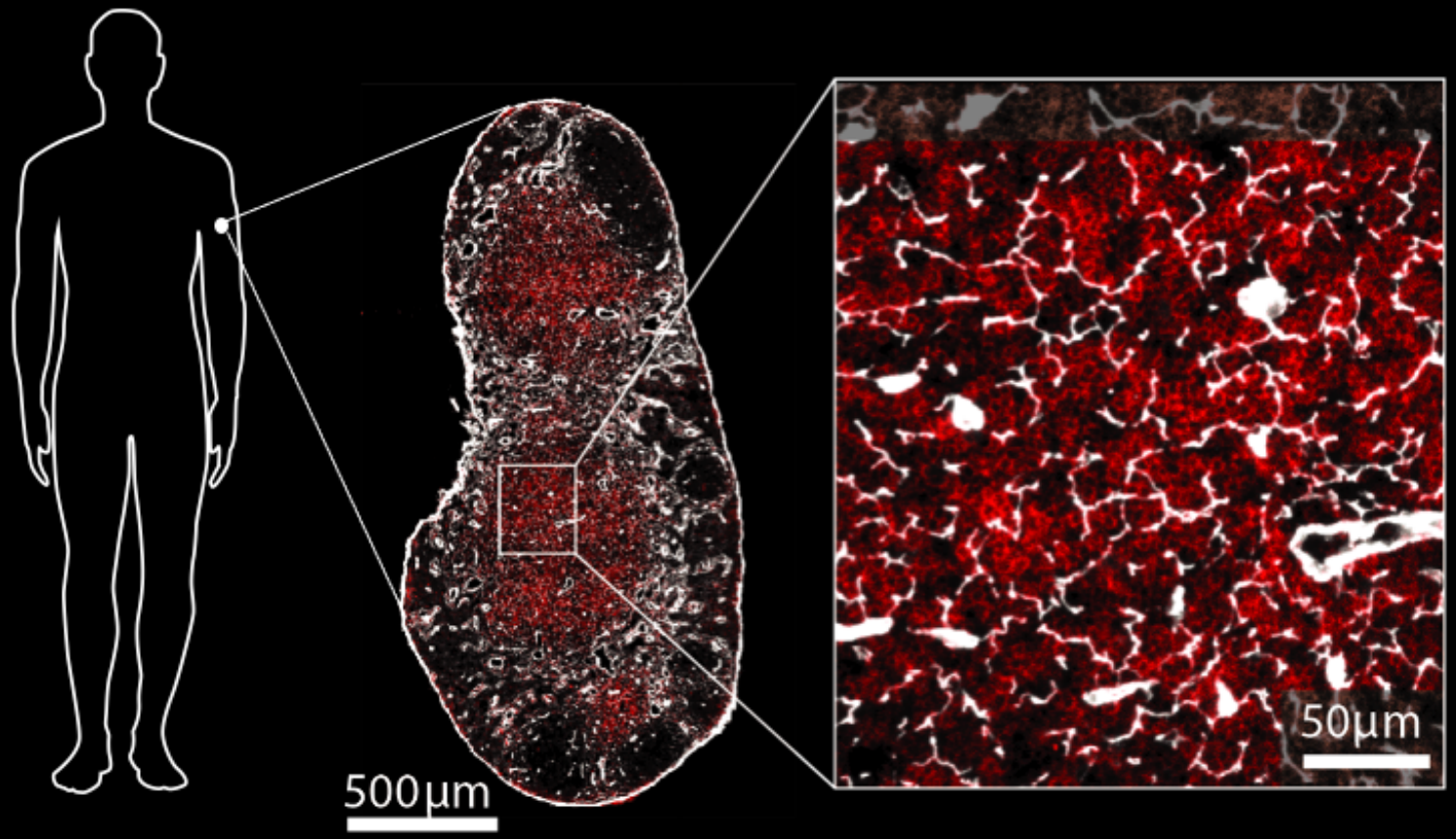
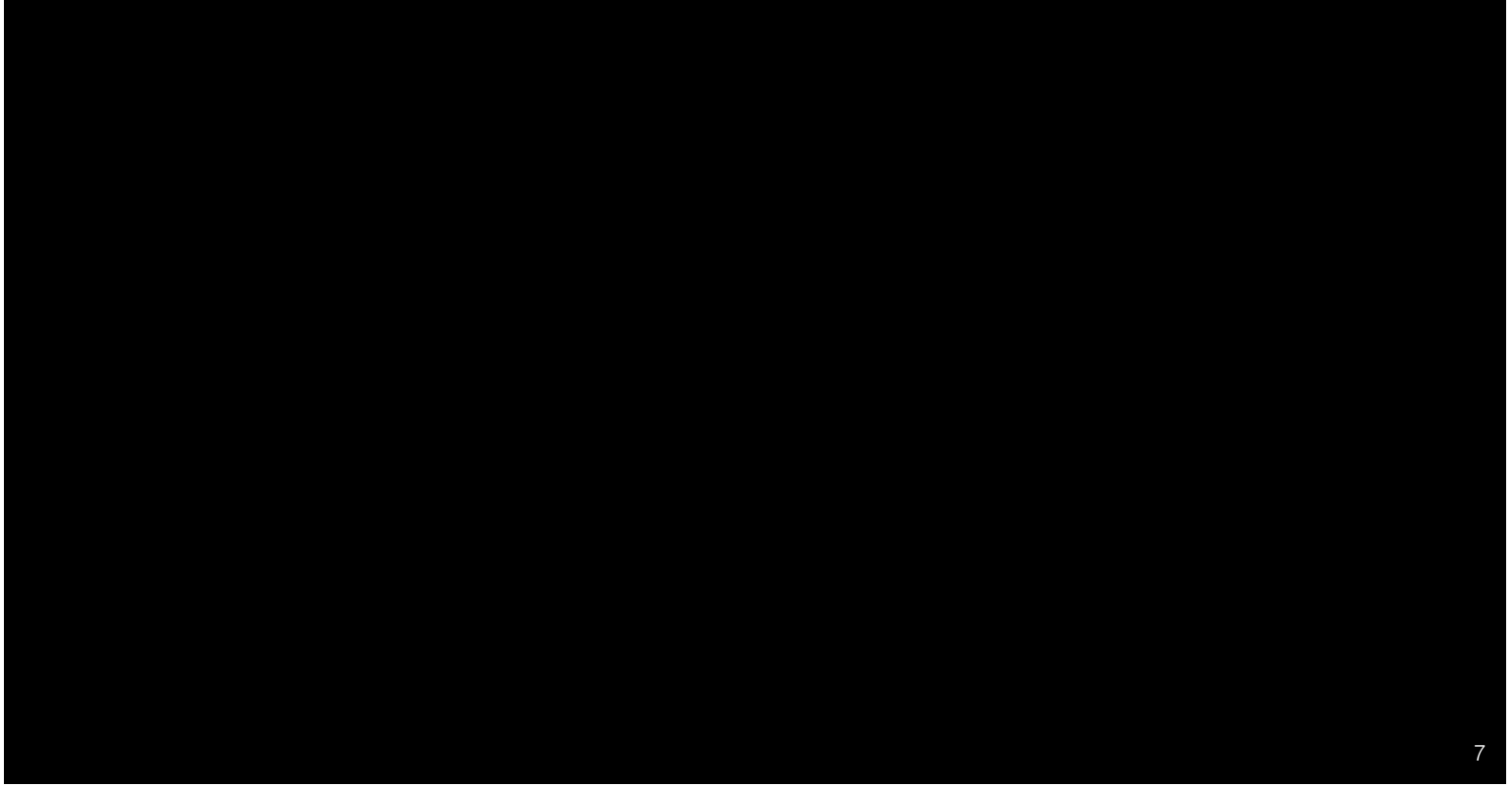
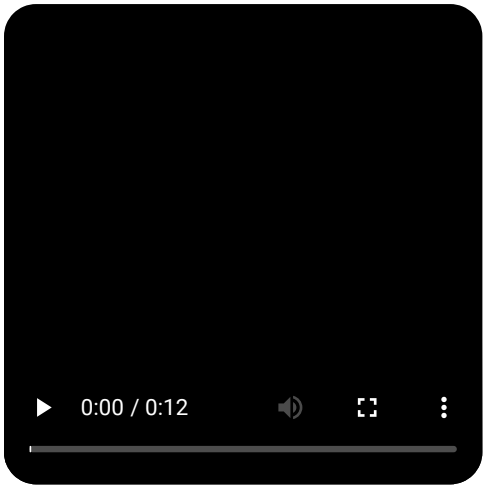


Image: Connie Shen & Judith Mandl.



The question: why no traffic jams?

?



How do T cells respond to complex and crowded environments, and does their smooth traffic flow ever break down?

Approach: mechanistic modelling.

"What I cannot create, I do not understand."

— Richard Feynman

"Creating" real and simulated T-cell crowds.

Put T cells in controlled environments, inspired by the physics field of **crowd dynamics**.

1. In silico: computational model
2. In vitro: controlled environment in the lab

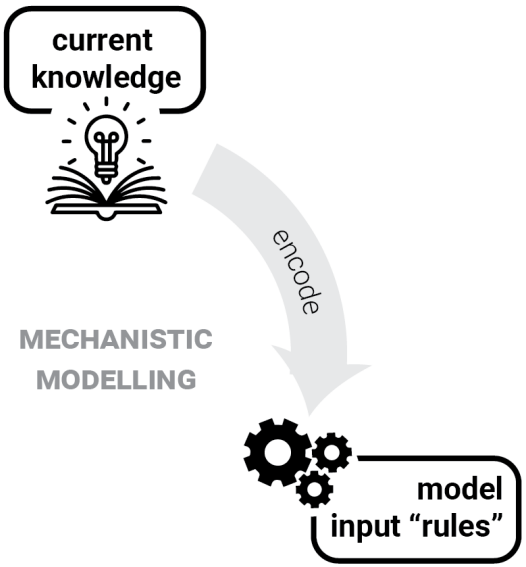
Can we "build a crowd" — i.e., can our model predict what real T cells will do *in vitro*?

Data: time-lapse imaging of moving cells.
Predictions: what will the crowd do?

The circle of ~~life~~ mechanistic modelling.

MECHANISTIC
MODELLING

The circle of ~~life~~ mechanistic modelling.



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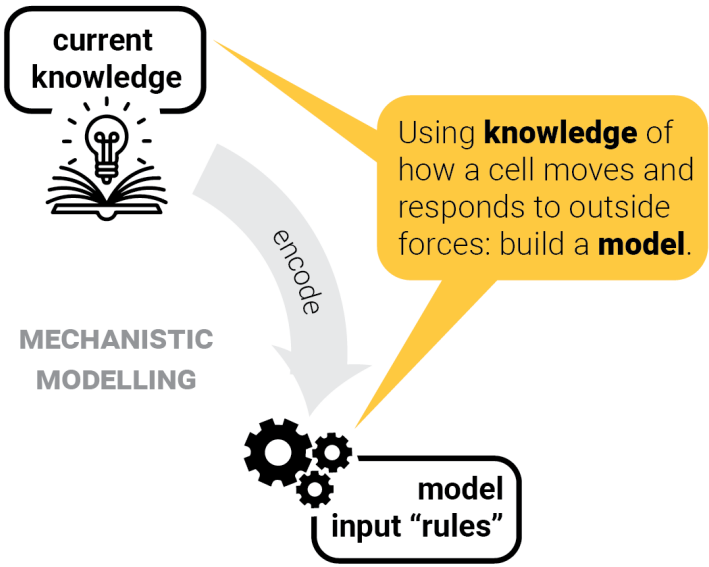

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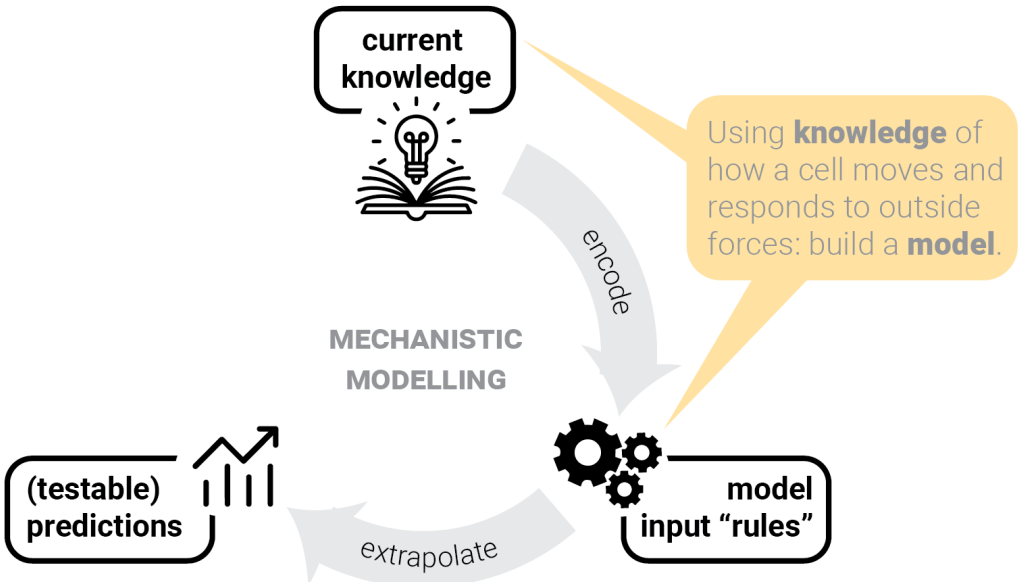

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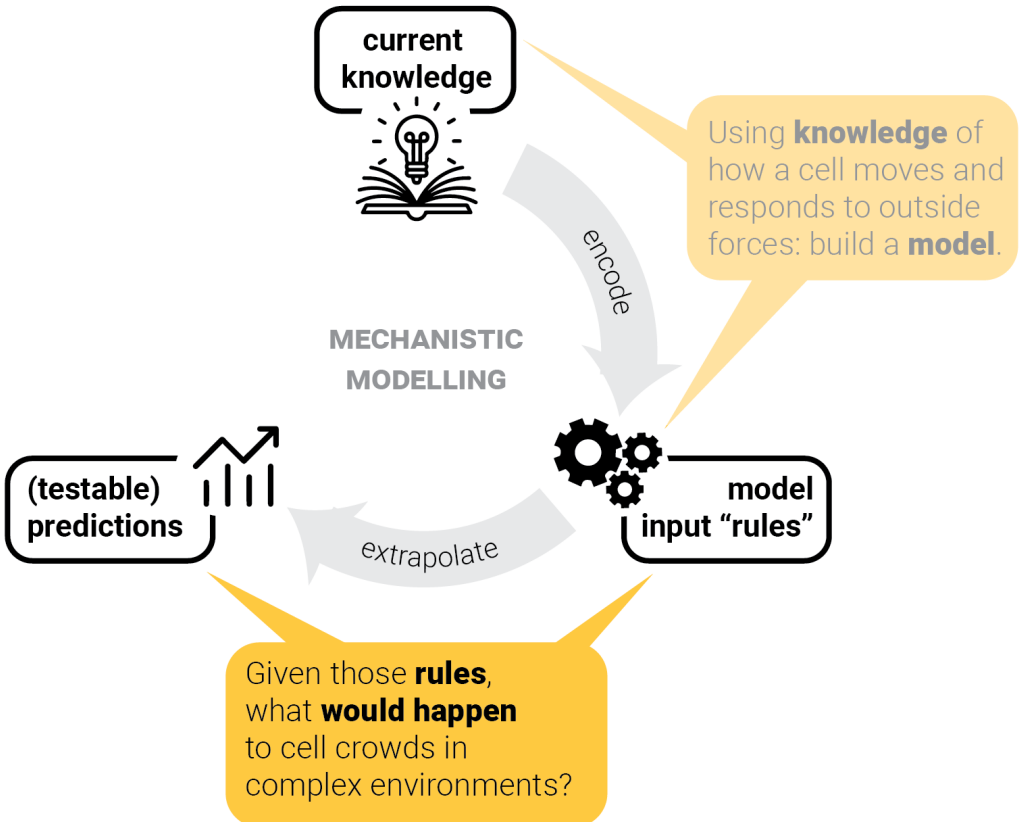

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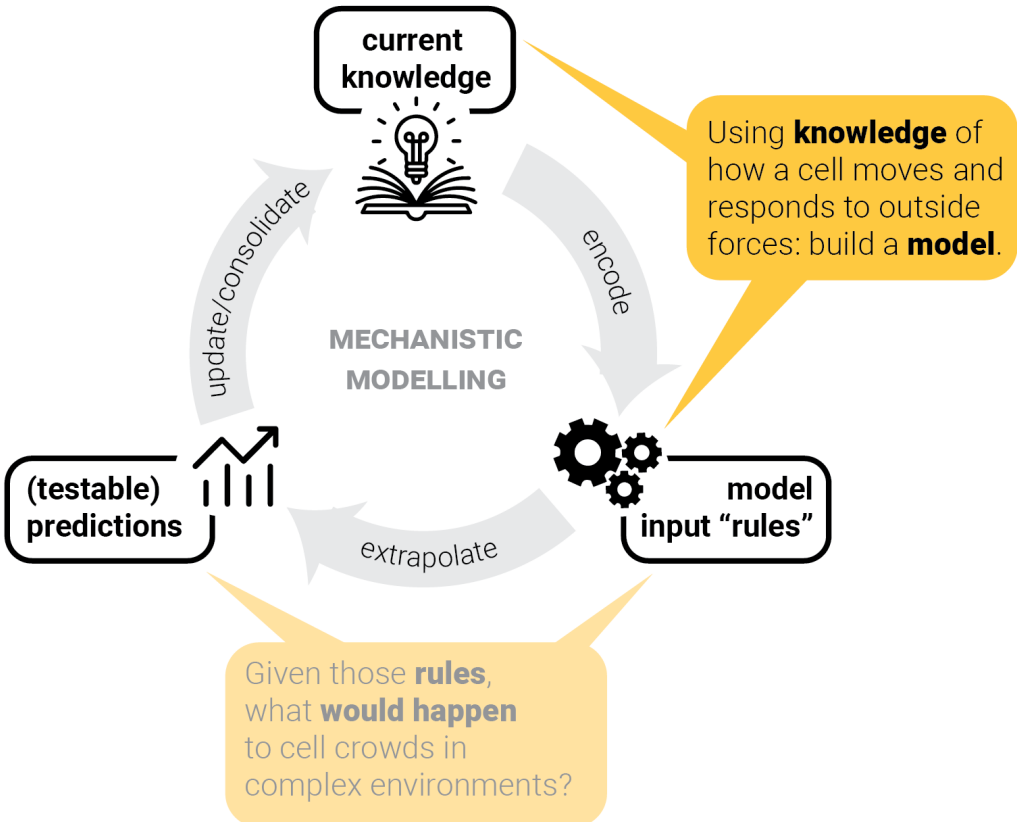

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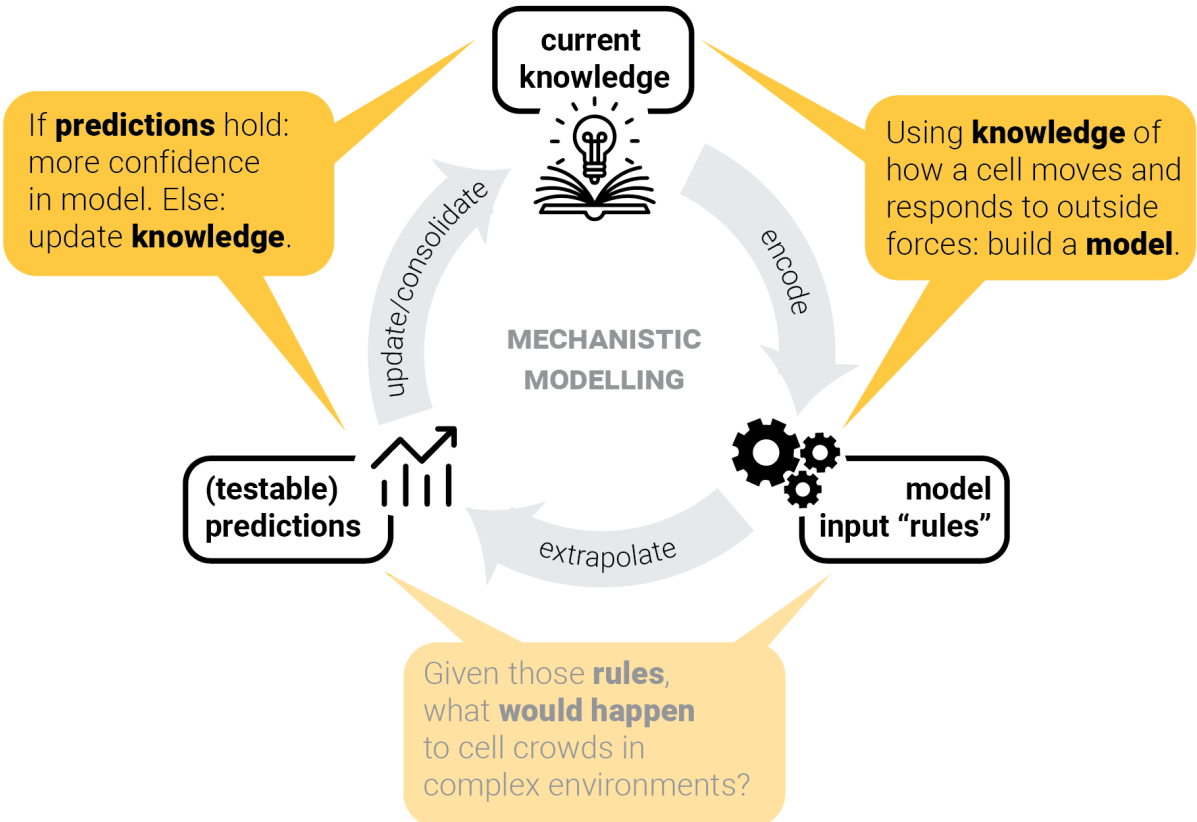

The role of predictions.

(Interpretable) AI

Mechanistic modelling

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Good predictions/decisions

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Black-box models: no knowledge gain (since we don't know *how* they work)

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Mechanistic modelling

Knowledge (or models of it)

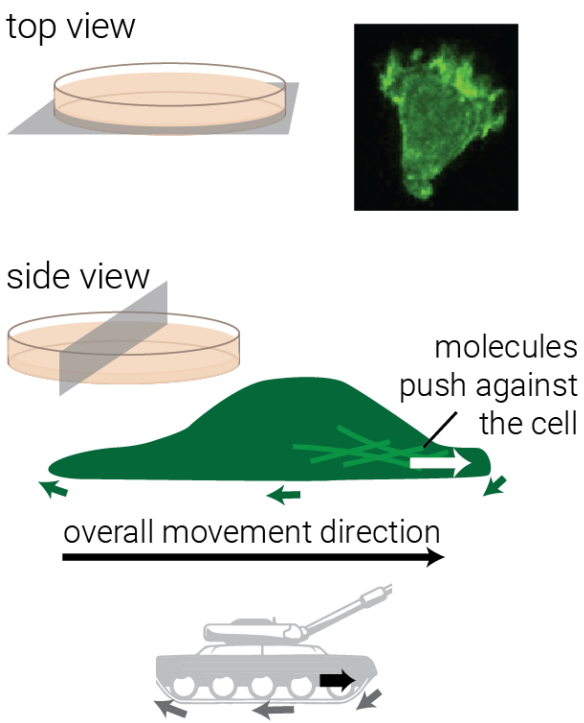
Predictions

Black-box models: no knowledge gain (since we don't know *how* they work)

Interpretability is critical to extract knowledge from mechanistic models.

Example:
T-cells in one lane traffic.

Step 1: gather input knowledge.



Adapted from: Dupré et al (2015). doi: 10.3389/fimmu.2015.00586.

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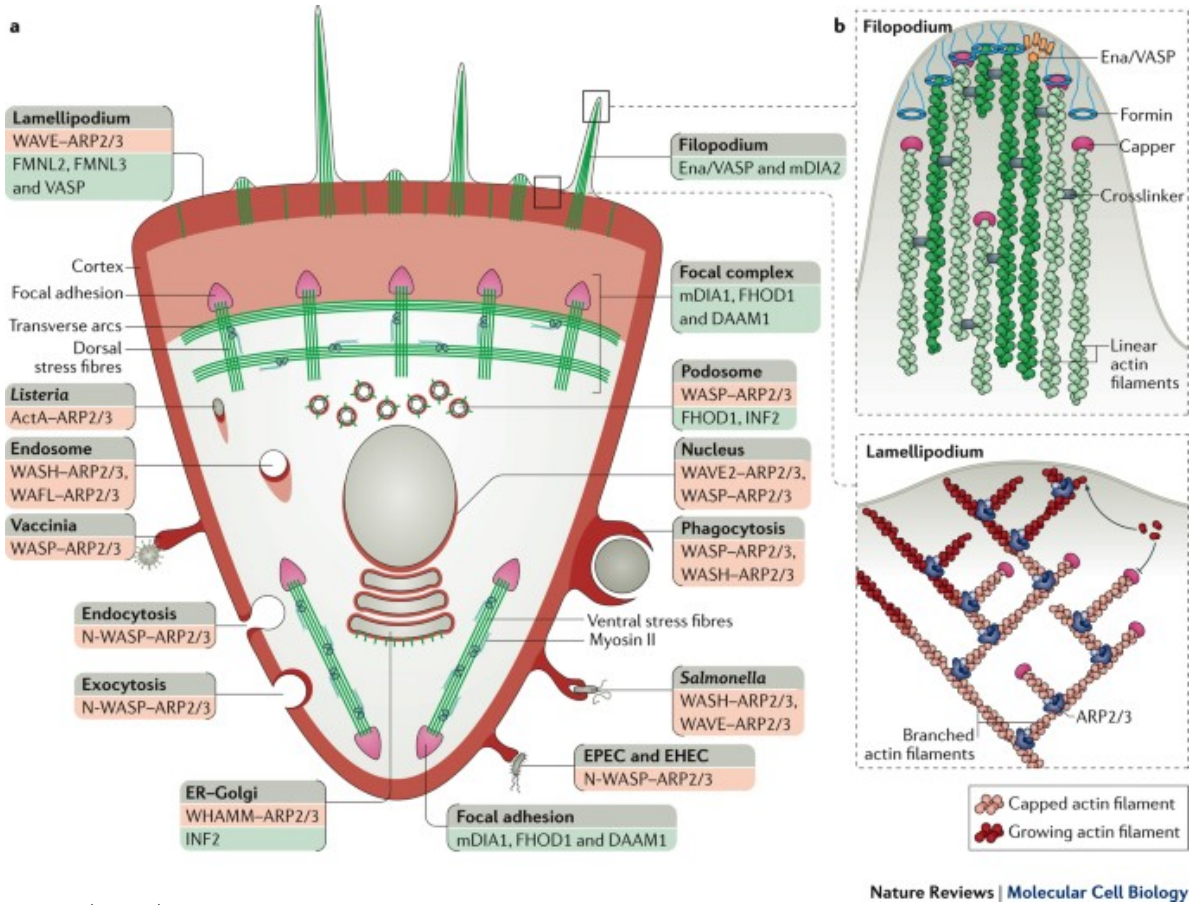
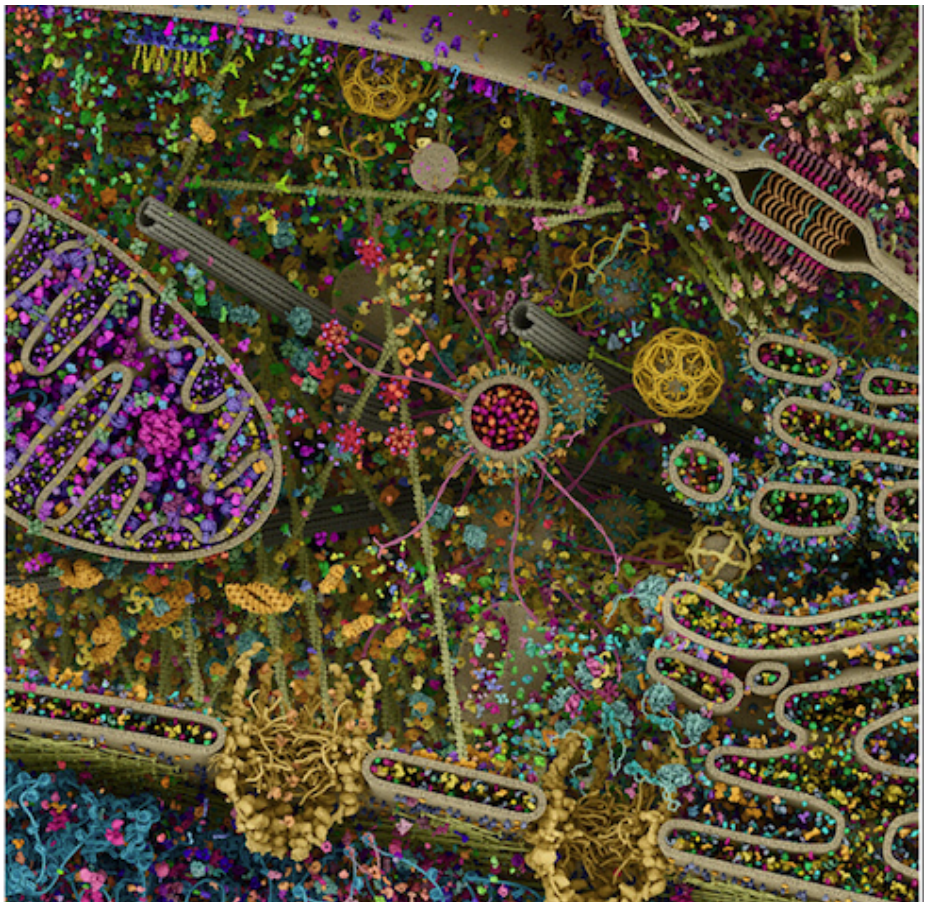


Carlier and Shekhar (2017). doi: 10.1038/nrm.2016.172.

Step 2: encode into a model.



Evan Ingersoll & Gaël McGill, Images from science 3 exhibition.

Option 1: Detailed model

Explicitly encode every molecule and resulting force.

\+ highly interpretable!

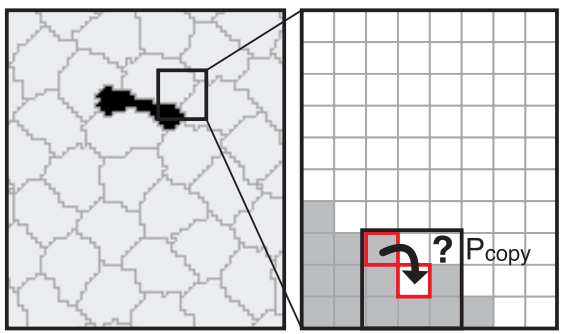
\+ **emergent** behavior.

– too expensive to model crowds.

Step 2: encode into a model.

Option 2: Phenomenological — Cellular Potts Model (CPM)[1]

Pixels belong to cells, which move by copying pixels:



$$P_{\text{copy}} = \begin{cases} e^{-\Delta H/T} & \Delta H > 0 \\ 1 & \Delta H \leq 0 \end{cases}$$

[1] Graner and Glazier (1992). doi:10.1103/PhysRevLett.69.2013

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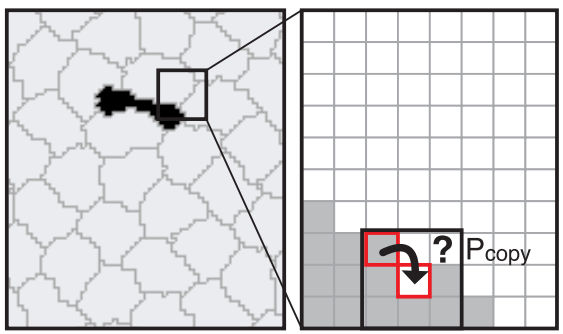

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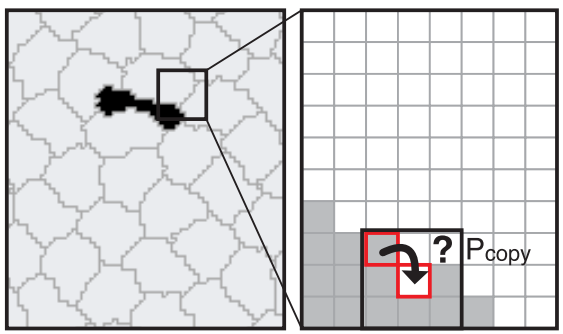

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→ Cells have shapes and interact naturally through **volume exclusion** (each pixel can only belong to one cell at a time). Crowd behavior still **emerges**.

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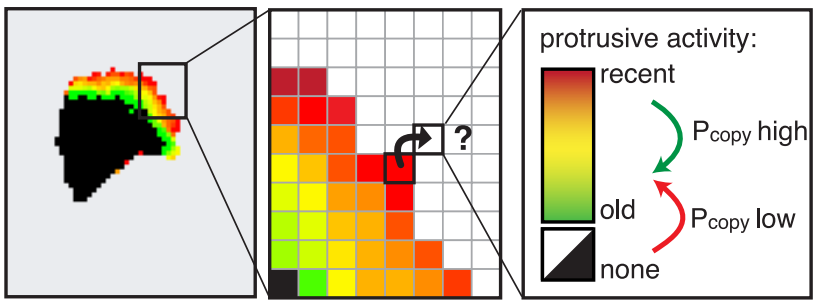
Step 2: encode into a model.

Cells move if we add **positive feedback** on protrusive **activity** (≈ actin polymerization)[1]:



Parameters:

λ_{act}	≈	protrusive force
max_{act}	≈	polymerized actin lifetime

→ realistic cell shape and motility [1,2].

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[1]Niculescu et al. (2015). doi:10.1371/journal.pcbi.1004280
[2]Wortel et al. (2021). doi:10.1016/j.bpj.2021.04.036

Step 3: predict crowd behavior.

A cornerstone scenario in **crowding physics**: one-lane traffic.

[1] John et al. (2009). doi:10.1103/PhysRevLett.102.108001
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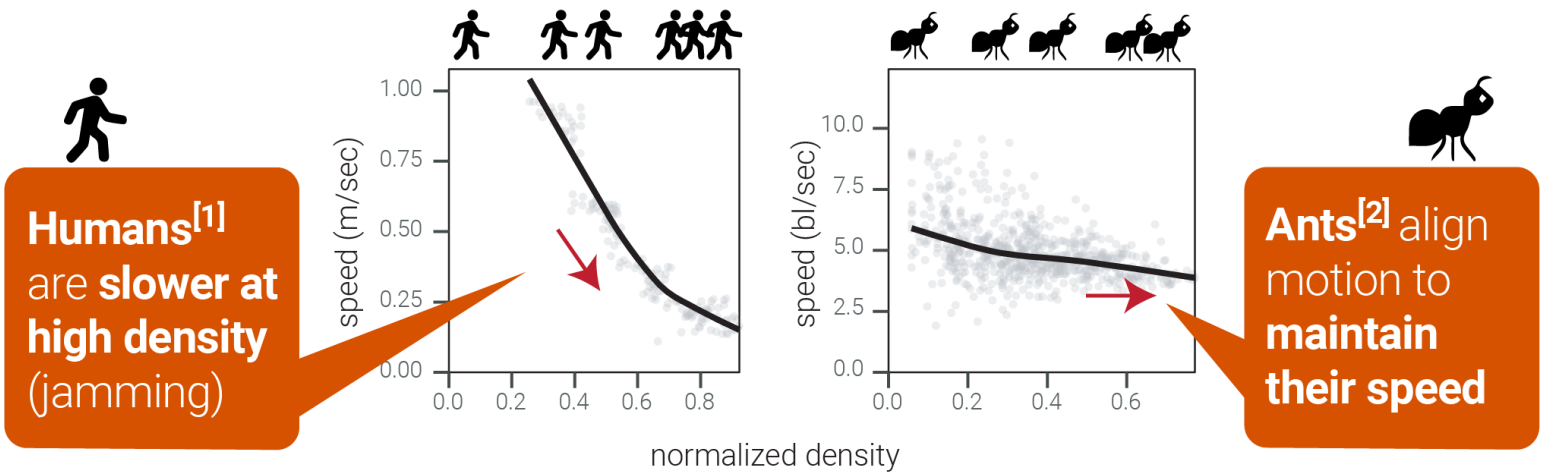

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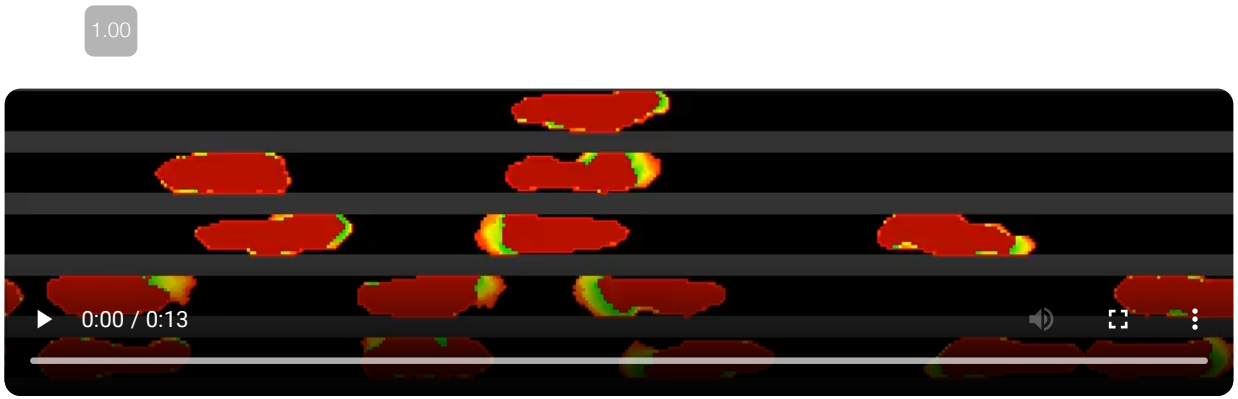
What do T cells do? Put single (CPM) cells **together** in **constrained channels** and predict crowd behavior:



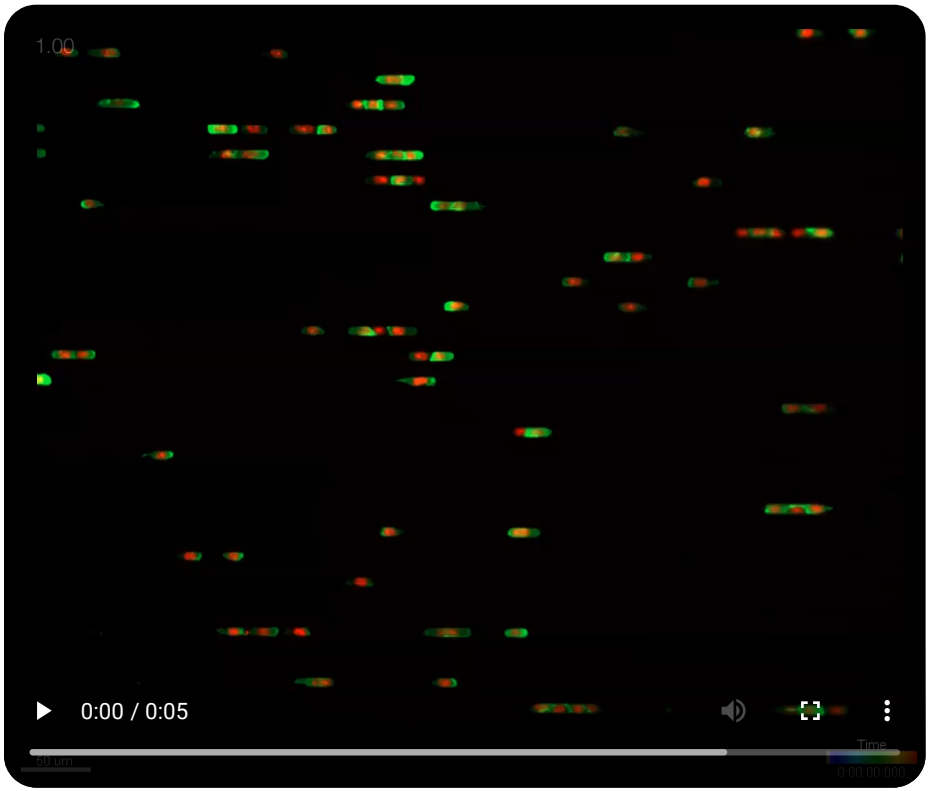
Step 3: predict crowd behavior.

What do T cells do? Put single (CPM) cells **together** in **constrained channels** and predict crowd behavior:

Qualitatively: cells rapidly align into "trains" to keep moving.

Step 4: test model predictions.

What about real T cells?



Data: Jérémy Postat and Judith Mandl.

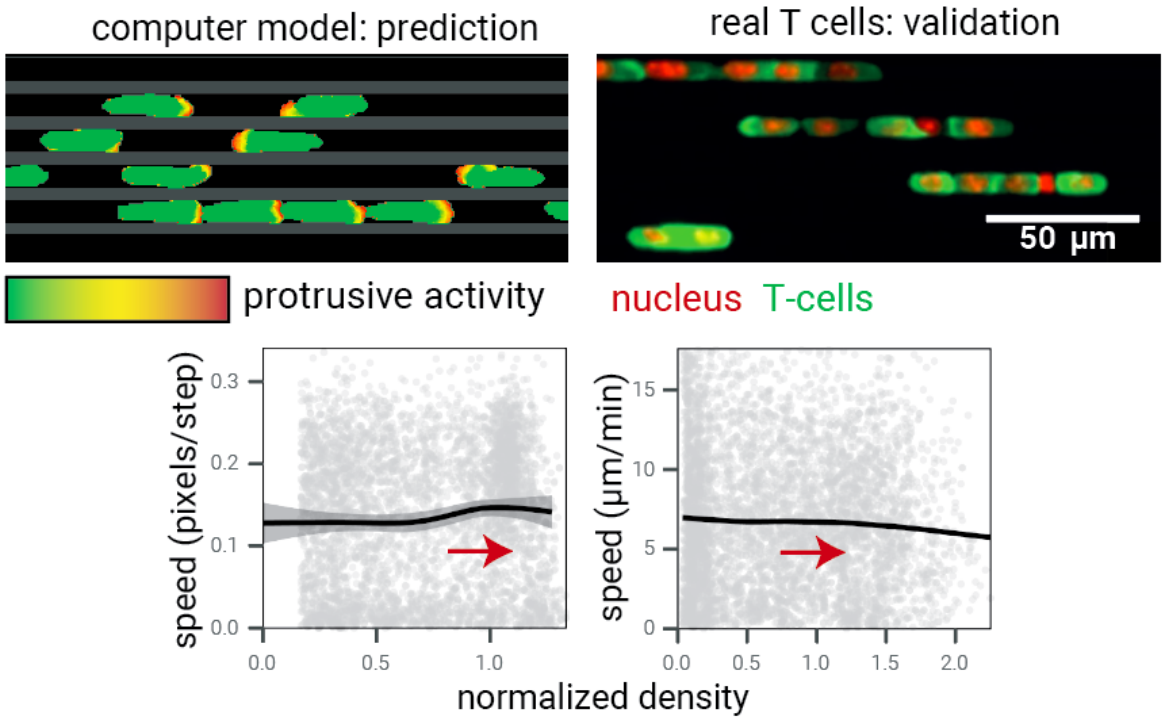
Step 4: test model predictions.

What about real T cells? **Again: train formation!**

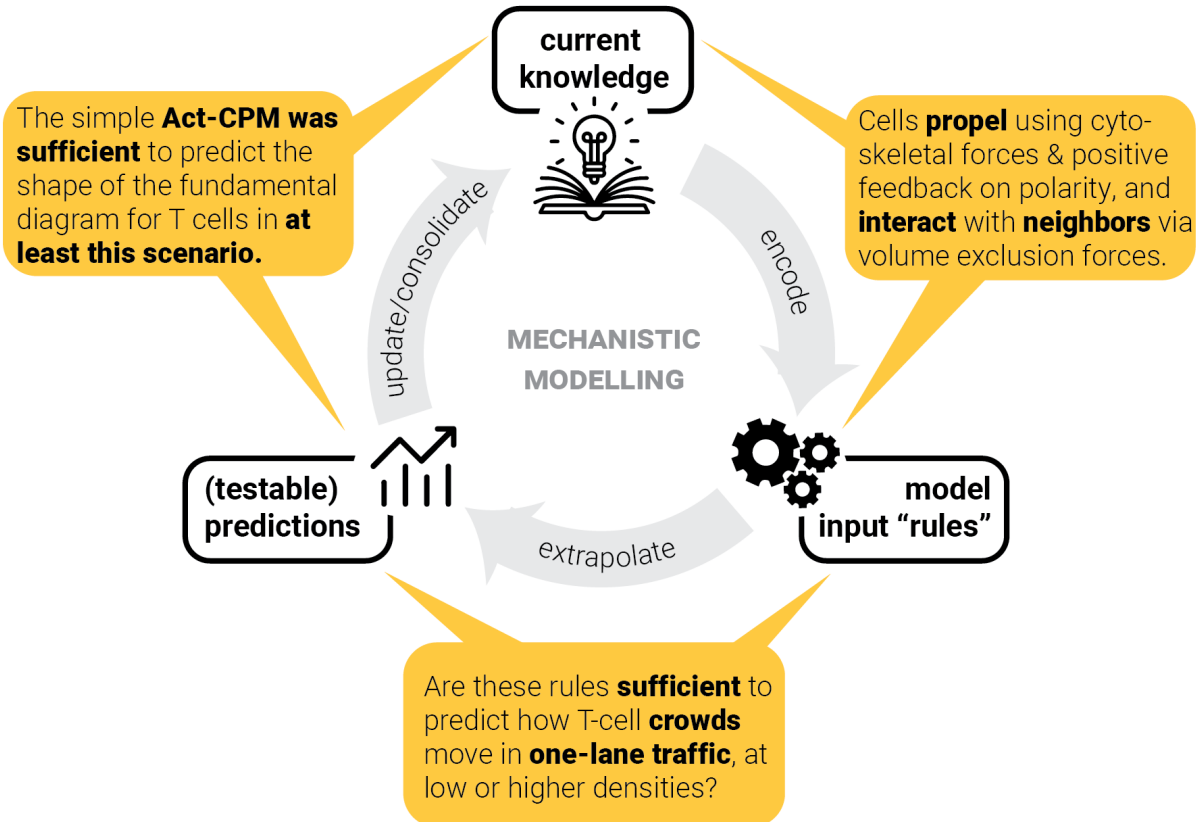
Data: Jérémy Postat and Judith Mandl.

Step 4: test model predictions.

Quantitatively: the fundamental diagram in both cases is flat.



Step 5: consolidate model — and repeat.



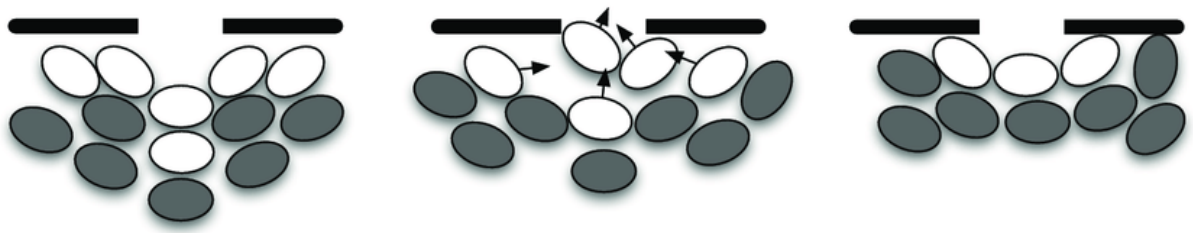
Step 5: consolidate model — and repeat.

Model consolidation != proof.

Can we predict crowd behavior in other scenarios as well?

Step 5: consolidate model — and repeat.

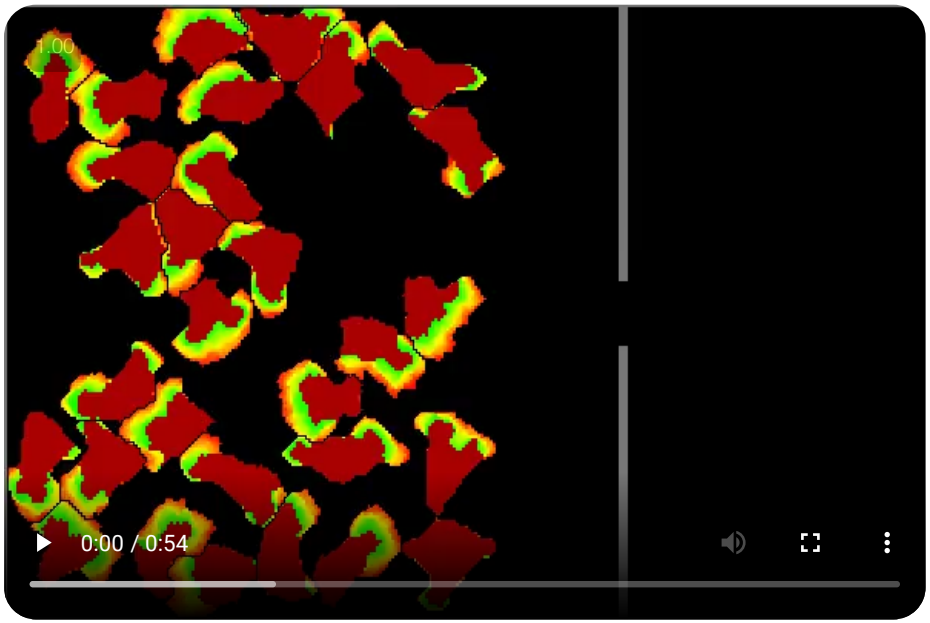
Pedestrian crowds can form **jamming arches** near an exit. This scenario is well-studied because of **crowd disasters**, such as at the Love Parade (Berlin, 2010).



→ What about T cells?

Step 5: consolidate model — and repeat.

Simulated T cells can indeed form jamming arches:



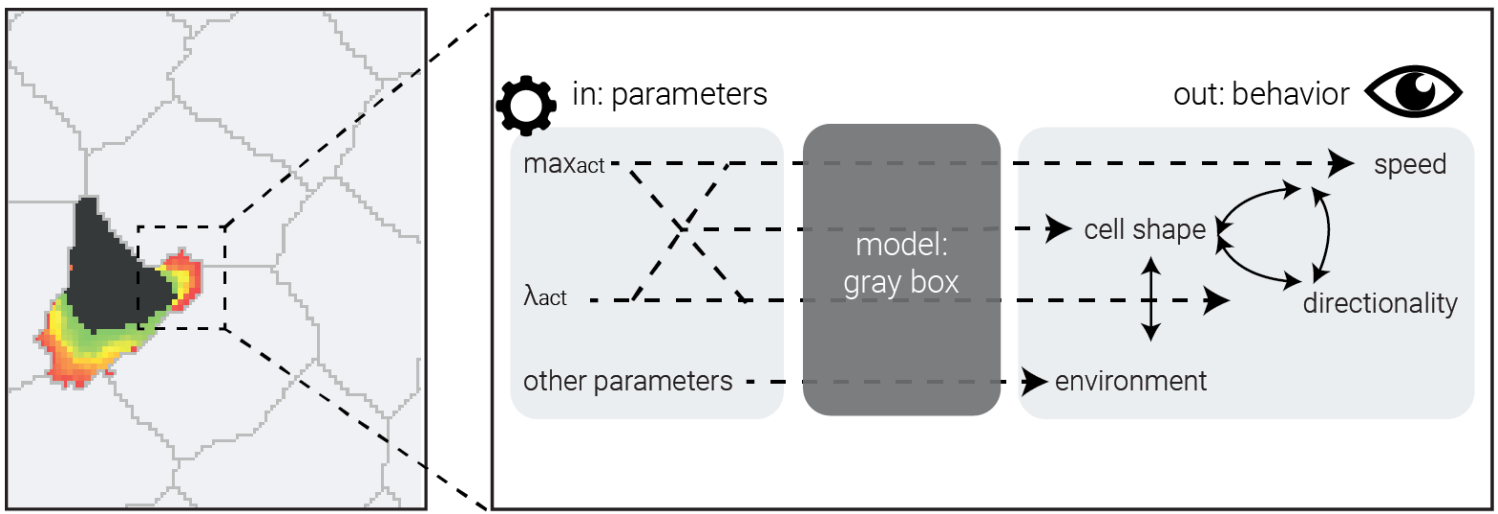
Work in progress, but see: Wortel (2021). https://repository.ubn.ru.nl/handle/2066/236680.

Work of Shabaz Sultan

Challenge:
Are CPMs interpretable?

CPMs are not fully interpretable.

Emergent behavior is nice, but...



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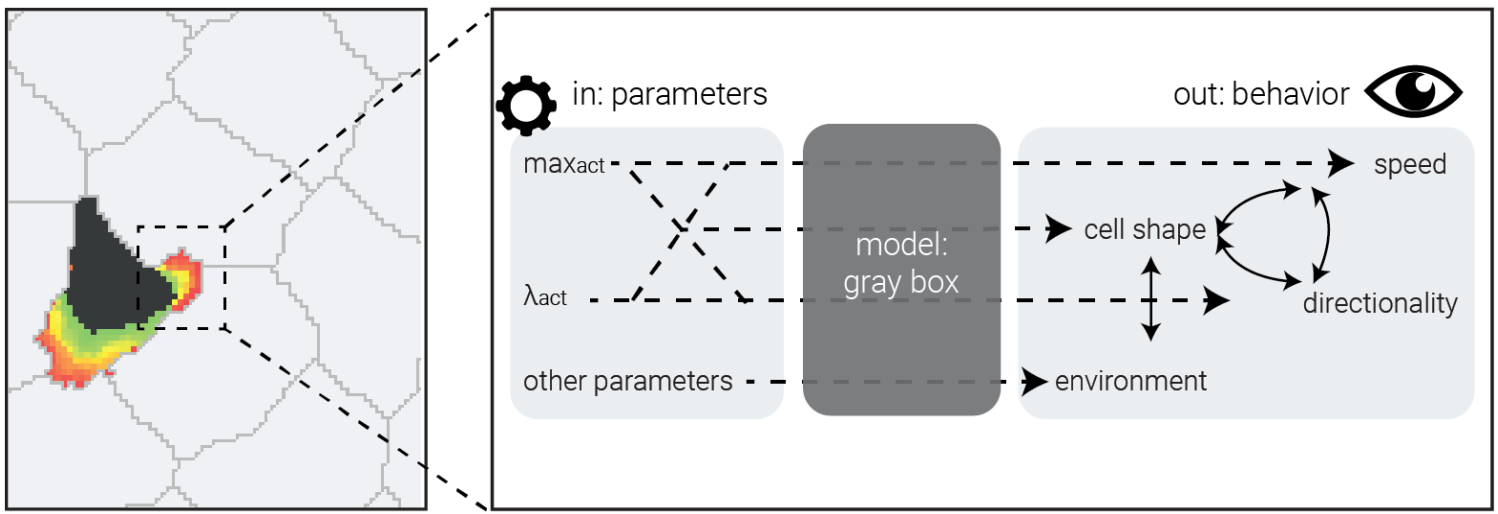
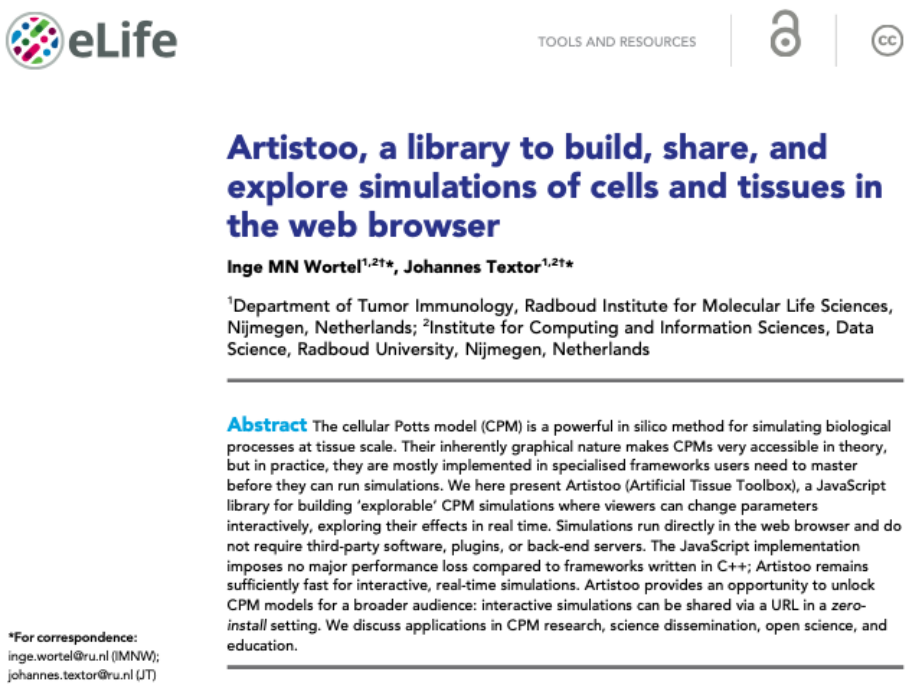


... we still don't know **exactly** how parameters lead to outputs.

"Explaining" CPMs — visualization

Visualizing and manipulating models interactively: artistoo.net



eLife

TOOLS AND RESOURCES

Artistoo, a library to build, share, and explore simulations of cells and tissues in the web browser

Inge MN Wortel[1,2†*], **Johannes Textor**[1,2†*]

[1]Department of Tumor Immunology, Radboud Institute for Molecular Life Sciences, Nijmegen, Netherlands; [2]Institute for Computing and Information Sciences, Data Science, Radboud University, Nijmegen, Netherlands

Abstract The cellular Potts model (CPM) is a powerful in silico method for simulating biological processes at tissue scale. Their inherently graphical nature makes CPMs very accessible in theory, but in practice, they are mostly implemented in specialised frameworks users need to master before they can run simulations. We here present Artistoo (Artificial Tissue Toolbox), a JavaScript library for building 'explorable' CPM simulations where viewers can change parameters interactively, exploring their effects in real time. Simulations run directly in the web browser and do not require third-party software, plugins, or back-end servers. The JavaScript implementation imposes no major performance loss compared to frameworks written in C++; Artistoo remains sufficiently fast for interactive, real-time simulations. Artistoo provides an opportunity to unlock CPM models for a broader audience: interactive simulations can be shared via a URL in a *zero-install* setting. We discuss applications in CPM research, science dissemination, open science, and education.

***For correspondence:**
inge.wortel@ru.nl (IMNW);
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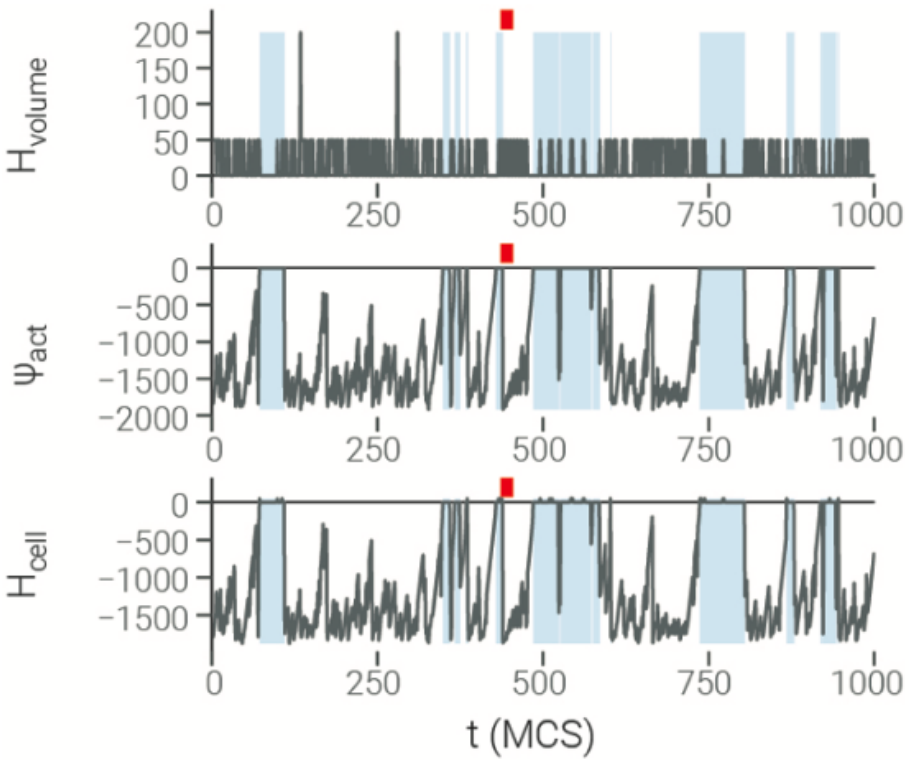
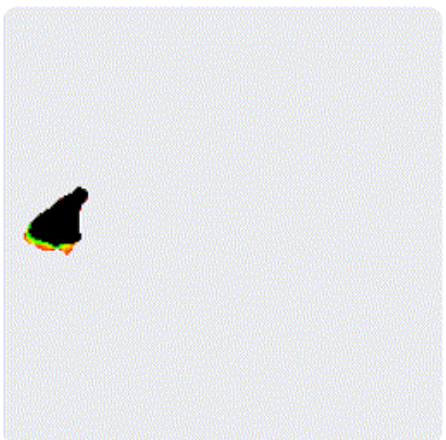
"Explaining" CPMs — tracking internal states

Tracking internal model states and outcomes over time:

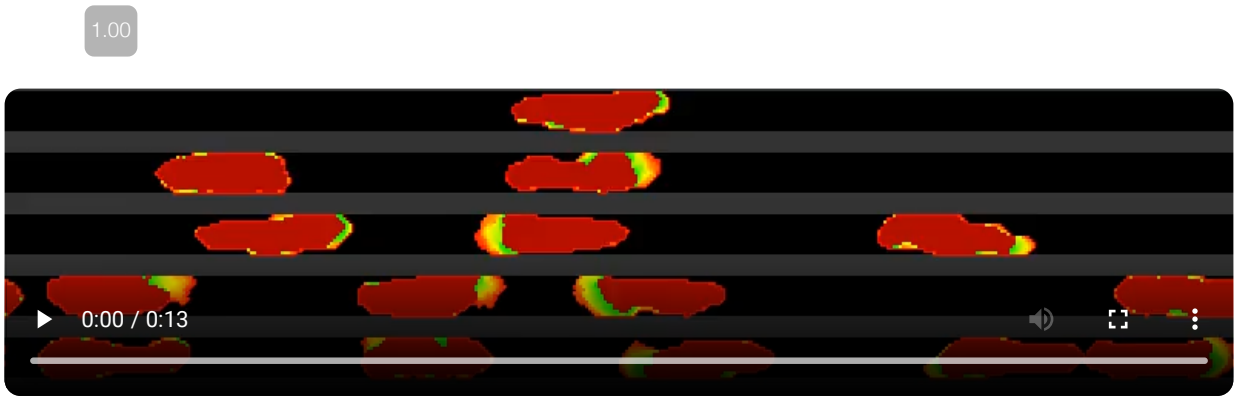


- competing energy terms (i.e.: maintaining volume, adhesion, protrusions, ...)
- protrusion activity
- cell breaking
- cell shape, speed, turning, ...



"Explaining" CPMs — parameter screening

For example: how does cell motion in a microchannel depend on channel size & cell flexibility (perimeter)?



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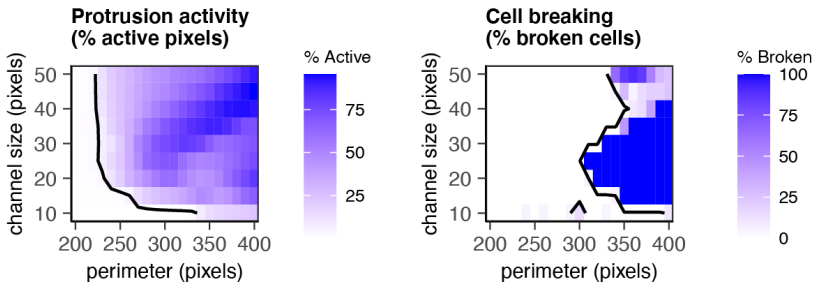

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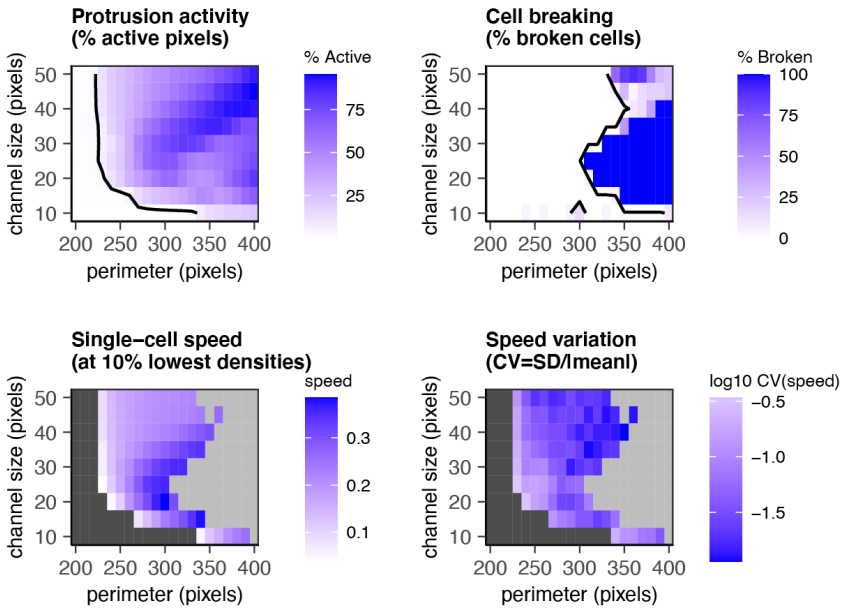

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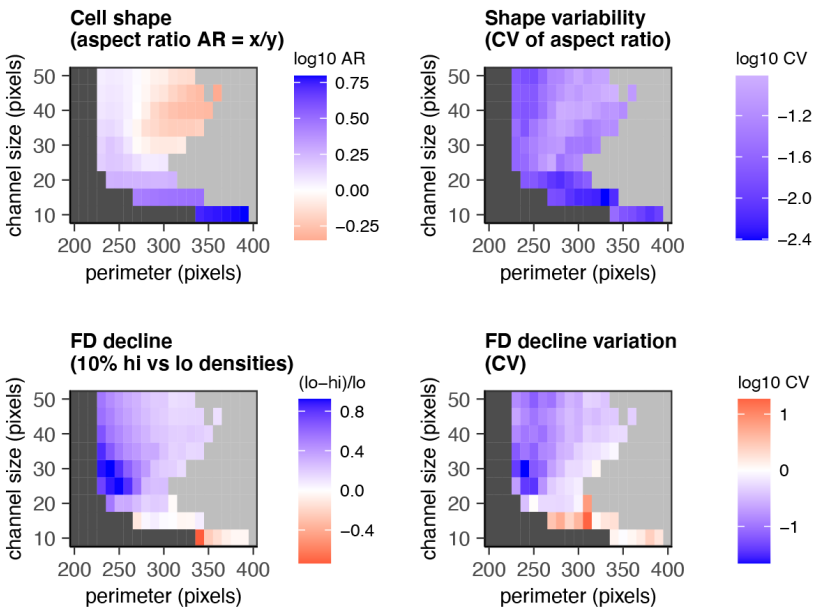

"What I cannot create, I do not understand."

— Richard Feynman

"What I cannot create, **visualize, and take apart**, I do not understand."

— Richard Feynman

Acknowledgments

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computational-immunology.org

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