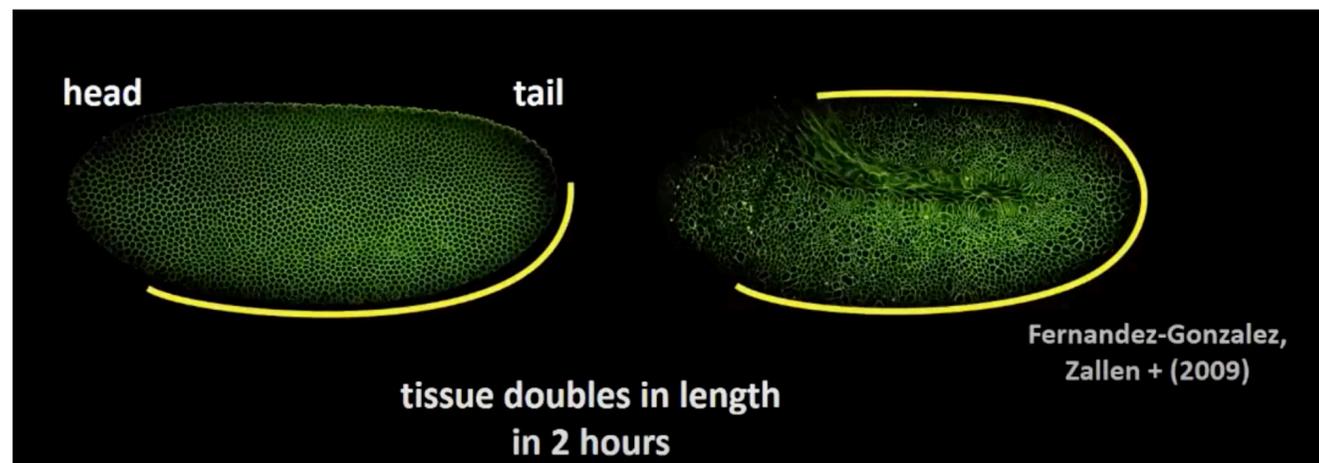# Tunable Matter for Life

Andrea J. Liu

University of Pennsylvania

head   tail

tissue doubles in length in 2 hours

Fernandez-Gonzalez, Zallen + (2009)
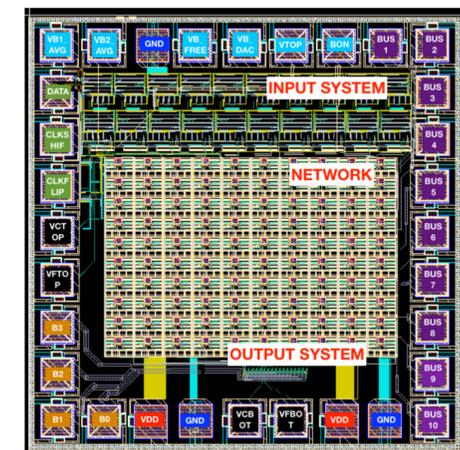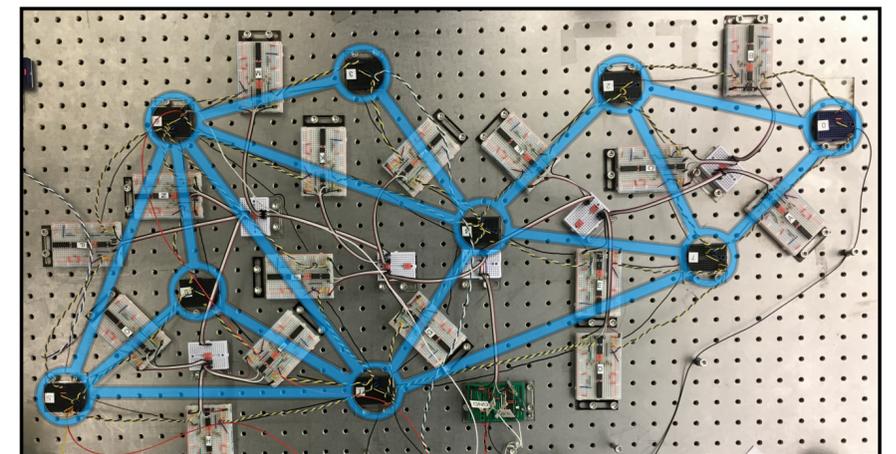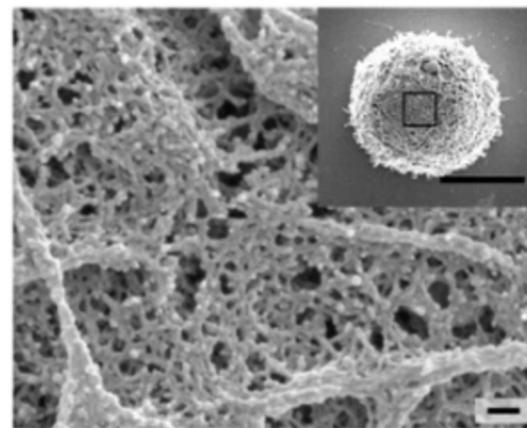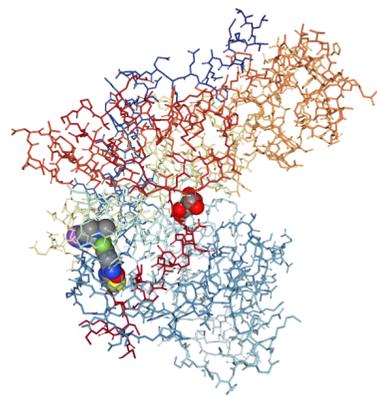
8 Things You Can Do

to Promote Human Rights in Science, Engineering, and Medicine

1. Highlight the Importance of Free Speech and the Dangers of Political Censorship for Work

2. Use your Expertise to Help Address Human Rights Challenges

3. Host a Discussion on Human Rights and/or Integrate Human Rights into your Teaching

4. Notify Human Rights Monitoring/Advocacy Bodies if you Suspect Rights Violations

5. Urge Institution to Assist Colleagues Fleeing Persecution Through Fellowships and Other Means

6. When Planning Travel, Learn about the State of Human Rights in your Destination

7. Write to U.S. or International Officials in Support of Colleagues

8. Stay Informed by Attending Human Rights Events

+ Ask me for this slide for you to share in your talks!

www.nationalacademies.org/8-things-you-can-do

https://rdcu.be/eIOdv

Leifer, Liu and Nagel
Nature, **641**, 592 (2025**)**

A Mystery of Life

- How do vast numbers of many different molecular components coordinate to produce organisms, not only in form but emergent, collective function?

- Biological systems are physical and must obey physical constraints

- But for function they must also obey design constraints

- Statistical physics: collective behavior with physical constraints but with few different components

- Biology: detailed networks of many different interacting components but not collective function

A Mystery of Life

- How do vast numbers of many different molecular components coordinate to produce organisms, not only in form but emergent, collective function?

- Biological systems are physical and must obey physical constraints

- But for function they must also obey design constraints

- Statistical physics: collective behavior with physical constraints but with few different components

- Biology: detailed networks of many different interacting components but not collective function

Need bridge between highly heterogeneous components with physical/design constraints and collective function

A Mystery of Life

- How do vast numbers of many different molecular components coordinate to produce organisms, not only in form but emergent, collective function?

- Biological systems are physical and must obey physical constraints

- But for function they must also obey design constraints

- Statistical physics: collective behavior with physical constraints but with few different components

- Biology: detailed networks of many different interacting components but not collective function

Need bridge between highly heterogeneous components with physical/design constraints and collective function

Why so much heterogeneity?

Condensed Matter and Tunable Matter

$$H = -\sum_{ij} J_{ij} S_i S_j$$

Fixed
interactions

1982 Nobel Wilson

2021 Nobel Parisi

spin systems
and beyond

Individually-adjustable
interactions

2024 Nobel Hopfield/Hinton

spin systems
and beyond

tunable matter

$$H = -\sum_{ij} J_{ij} S_i S_j$$

Fixed interactions

"More is Different"

But many more nearly same as more

Tunable Matter

$$H = -\sum_{ij} J_{ij} S_i S_j$$

Fixed
interactions

Individually-adjustable
interactions

"More is Different"
But many more nearly
same as more

Many more is more different

neural networks, brains

$$H = -\sum_{ij} J_{ij} S_i S_j$$

Fixed
interactions/
interaction
potentials

Dictated by
physics/chemistry

Tunable Matter

$$H = -\sum_{ij} J_{ij} S_i S_j$$

Fixed interactions/ interaction potentials

Dictated by physics/chemistry

Individually-adjustable interactions

Effective interactions characterized by tunable degrees of freedom

Why make interactions tunable?

Complex functionality

e.g. biological function

$$H = -\sum_{ij} J_{ij} S_i S_j$$

heterogeneity

Fixed interactions/ interaction potentials

Dictated by physics/chemistry

Individually-adjustable interactions

Effective interactions characterized by tunable degrees of freedom

Why make interactions tunable?

Complex functionality

e.g. biological function

Learning from Neural Networks
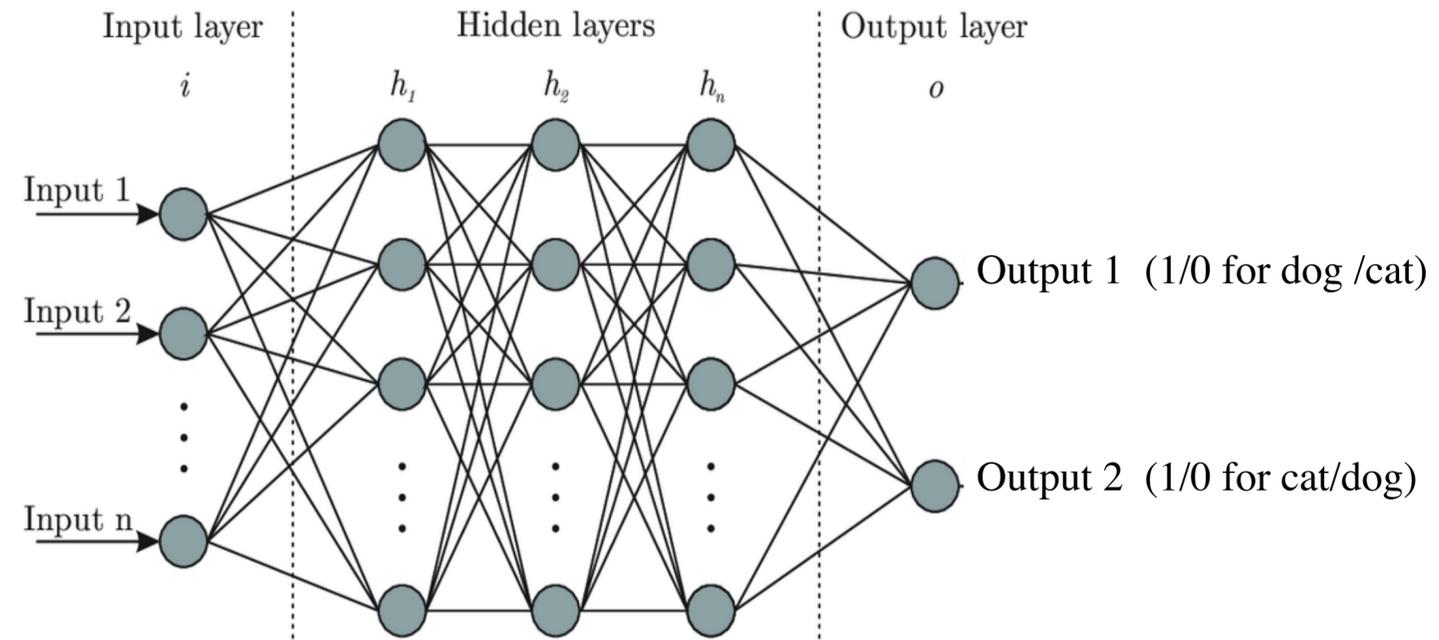
- Network parameters (tunable degrees of freedom) are adjusted to give desired output

- How to adjust?

$$\mathcal{C} = \sum_i (\text{desired output}_i - \text{free output}_i)^2$$

  – Minimize $\mathcal{C}$ by adjusting tunable DOF

Why is Many More Different in Neural Networks?
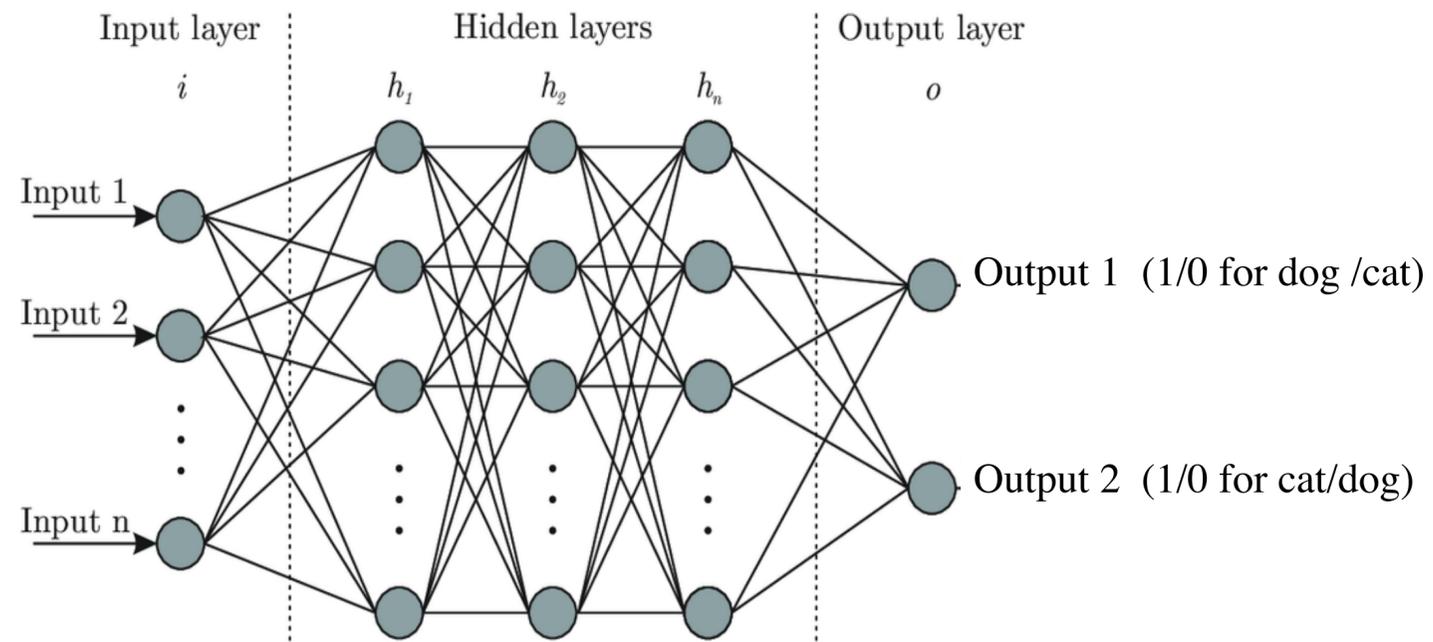
- Network tunable DOF are adjusted to give desired output

- How to adjust?

  – Evaluate cost function $\mathcal{C} = \sum_i (\text{desired output}_i - \text{free output}_i)^2$

  – Minimize $\mathcal{C}$ by adjusting tunable DOF

- \# constraints that can be satisfied increases with \# tunable DOF

- Many more is different bc \# tunable DOF increases with system size

Random Constraint-Satisfaction Problems

Can satisfy constraints
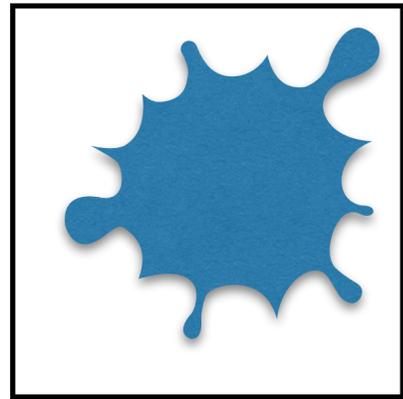
Can't satisfy constraints

non-universal stuff

over-parameterized

under-parameterized

$$\frac{\# \text{ constraints}}{\# \text{ tunable DOF}} \ll 1$$
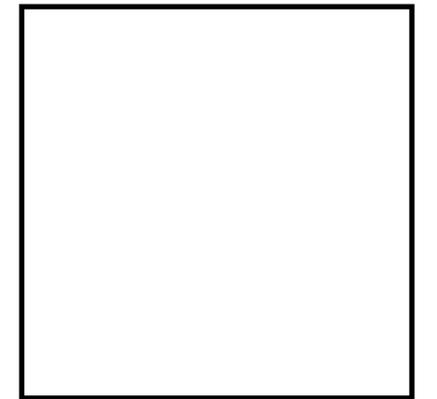
$$\frac{\# \text{ constraints}}{\# \text{ tunable DOF}} \sim 1$$

$$\frac{\# \text{ constraints}}{\# \text{ tunable DOF}} \gtrsim 1$$

- Modern AI operates in over-parameterized regime
  - Easy/fast to find global minimum
  - Training is robust to many parameter changes
  - Many good solutions

Gradient Descent is Great! BUT…

- Requires precise and complete microscopic knowledge of network to calculate cost function

- Requires calculation of direction of gradient descent

- Requires ability to modify individual edges of network

- Design by minimizing cost function is inherently global and therefore requires processor

Gradient Descent is Great! BUT…

- Requires precise and complete microscopic knowledge of network to calculate cost function

- Requires calculation of direction of gradient descent

- Requires ability to modify individual edges of network

- Design by minimizing cost function is inherently global and therefore requires processor

Can tunable degrees of freedom be adjusted for desired collective response without a processor?
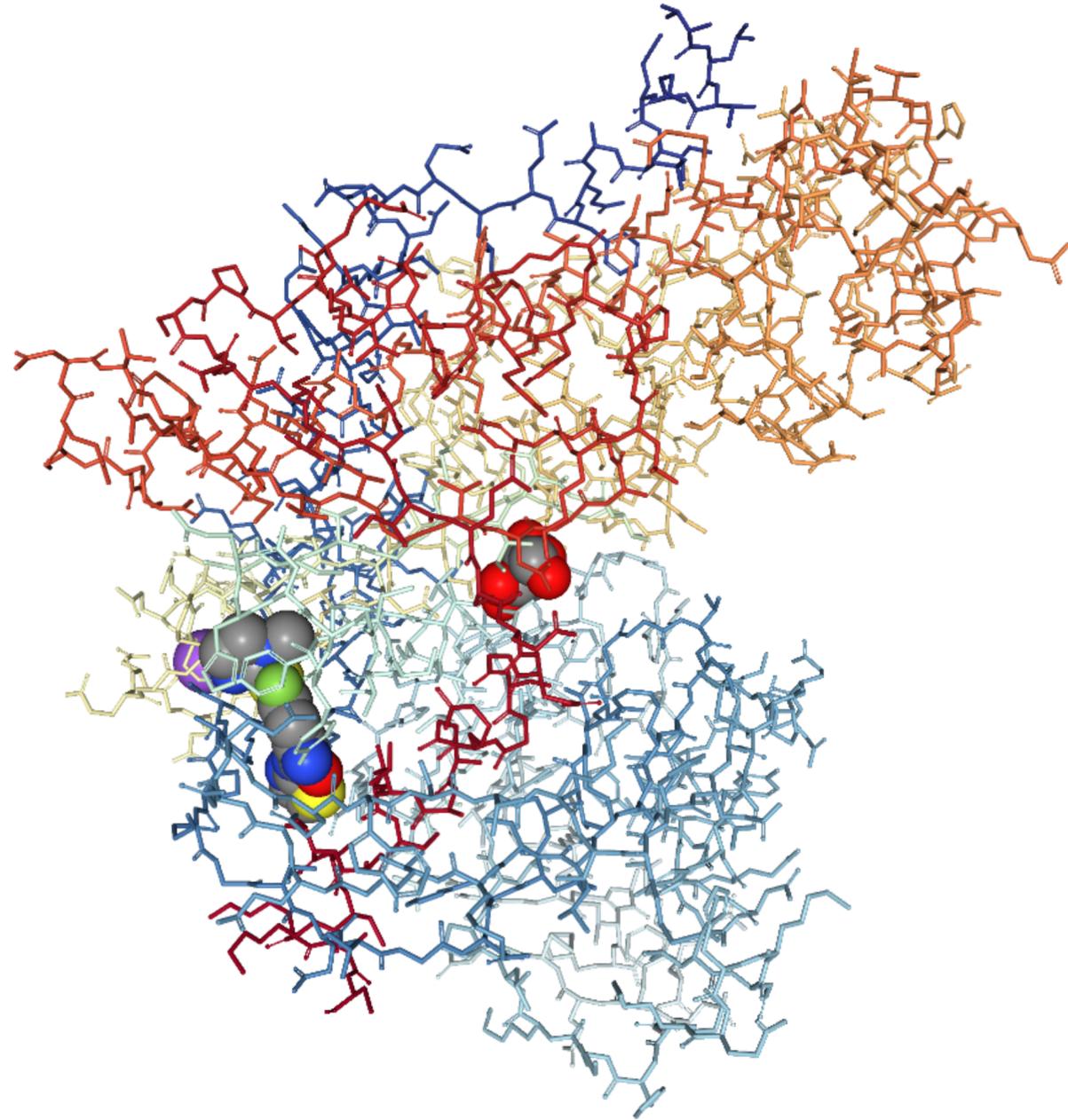
- Tunable DOFs: choice of amino acid at each point in sequence

- Physical DOFs: amino acid positions/ orientations/conformations

- Double optimization: tunable DOFs satisfy functionality, physical DOFs minimize free energy

Rocks, Pashine, Goodrich, Bischofberger, Liu, Nagel PNAS 2017
Rocks, Ronellenfitsch, Liu, Nagel, Katifori PNAS 2019
Hexner, Liu, Nagel PNAS (2020)
Stern, Hexner, Rocks, Liu PRX (2021)
Rouviere, Ranganathan, Rivoire, PRX Life (2023)
Rocks, Katifori, Liu arXiv (2024)
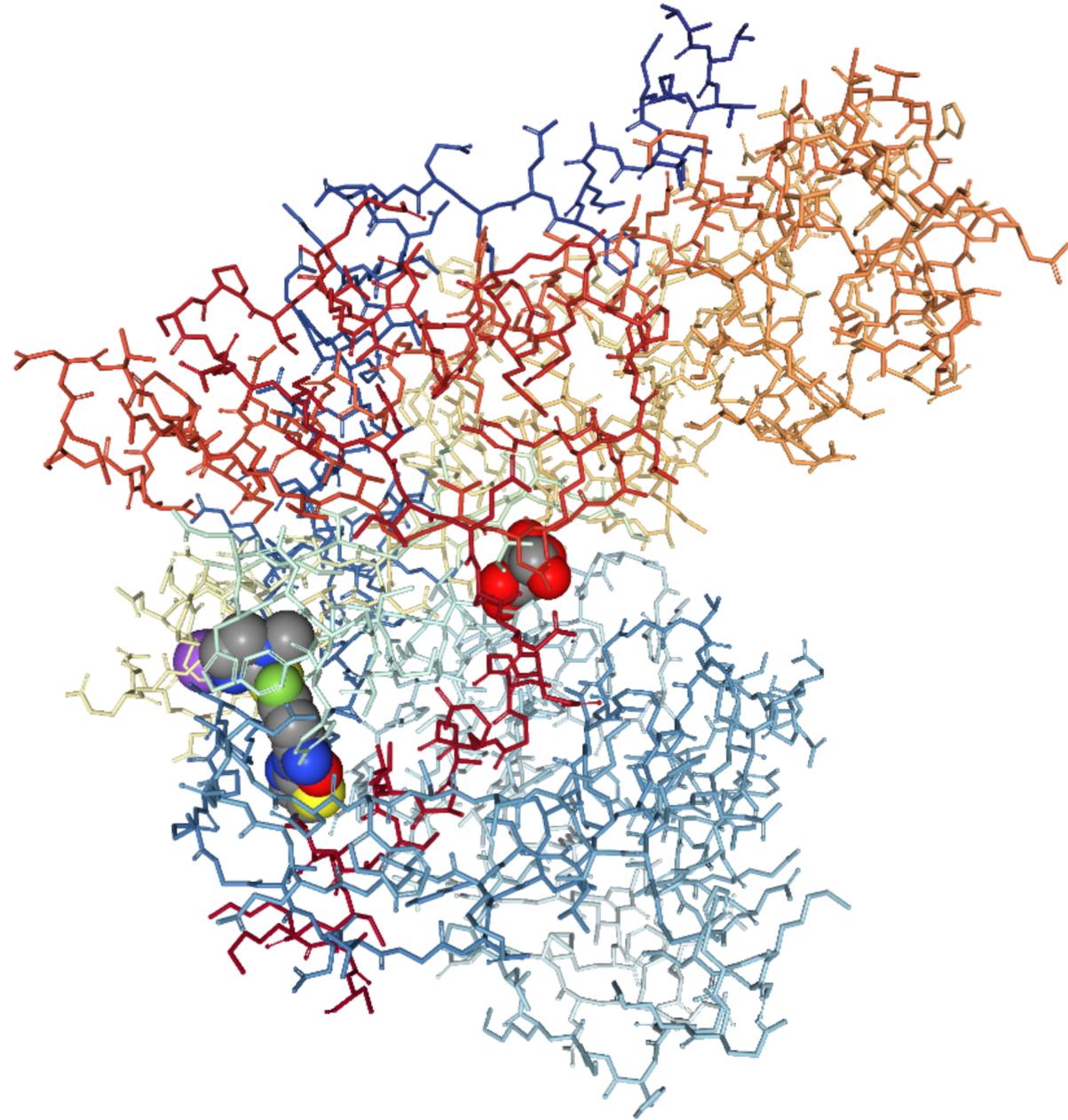
- **Tunable** DOFs: choice of amino acid at each point in sequence **heterogeneity!**

- **Physical** DOFs: amino acid positions/orientations/conformations

- **Double optimization:** tunable DOFs satisfy functionality, physical DOFs minimize free energy

Rocks, Pashine, Goodrich, Bischofberger, Liu, Nagel PNAS 2017
Rocks, Ronellenfitsch, Liu, Nagel, Katifori PNAS 2019
Hexner, Liu, Nagel PNAS (2020)
Stern, Hexner, Rocks, Liu PRX (2021)
Rouviere, Ranganathan, Rivoire, PRX Life (2023)
Rocks, Katifori, Liu arXiv (2024)

Are Proteins Over-Parameterized?

Can satisfy constraints
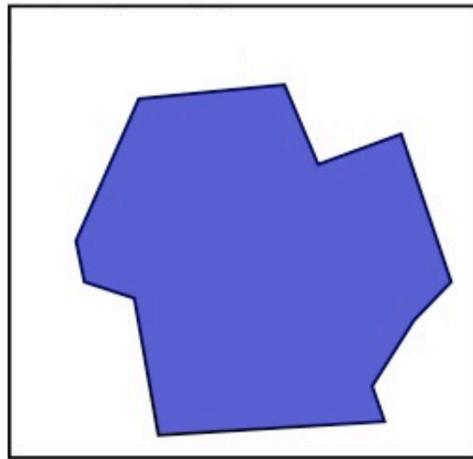
Can't satisfy constraints

non-universal stuff

over-parameterized

under-parameterized

$$\frac{\#\ \text{constraints}}{\#\ \text{tunable DOF}} \ll 1$$
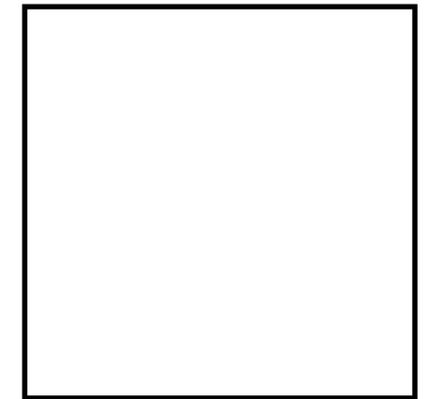
$$\frac{\#\ \text{constraints}}{\#\ \text{tunable DOF}} \sim 1$$

$$\frac{\#\ \text{constraints}}{\#\ \text{tunable DOF}} \gtrsim 1$$

- # tunable DOFs is extensive in length of sequence

- Easy/fast to find global minimum

- Generalizable: many mutations do not affect protein function

- Many good solutions: phenotypic convergence

Yes—by Evolution

- Evolution is great!
- But…
- It is very slow, requiring many generations

Yes—by Evolution

- Evolution is great!
- But…
- It is very slow, requiring many generations

Can tunable degrees of freedom be adjusted for desired collective response without a processor on time scales fast compared to evolution?

Epithelial Tissues during Development
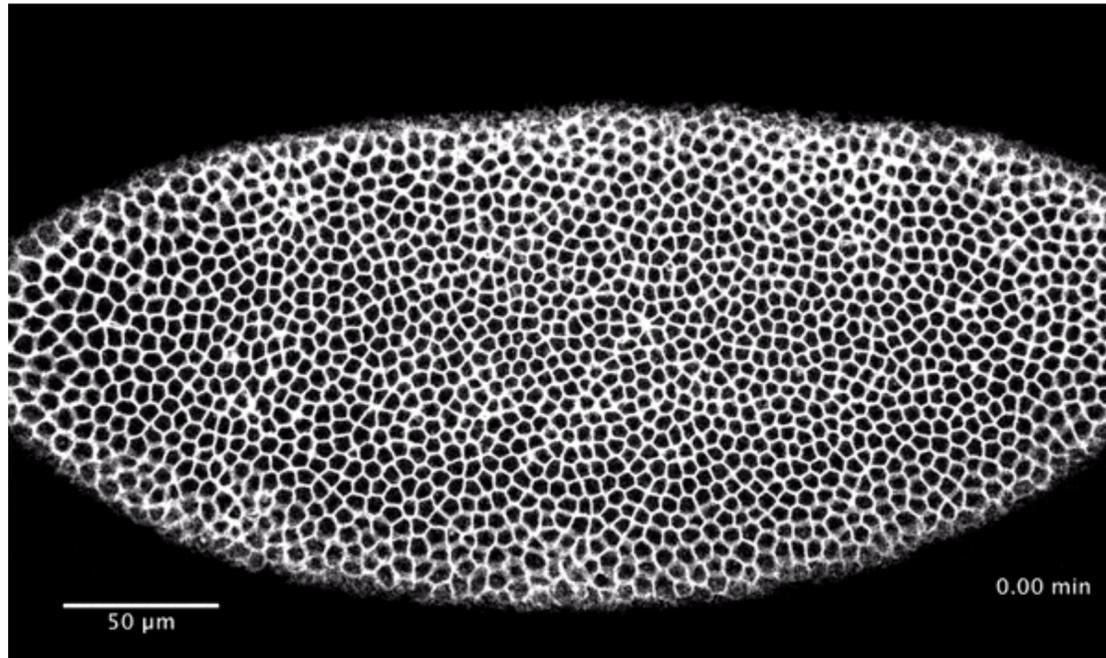
Tah, Härtter, Crawford, Kiehart, Schmidt, Liu (2024)
Arzash, Tah, Liu, Manning (2024)
Arzash, Liu Manning

- **Function**: tissue doubles in length in 2 hours at fixed area

head   tail

tissue doubles in length
in 2 hours

Fernandez-Gonzalez,
Zallen + (2009)
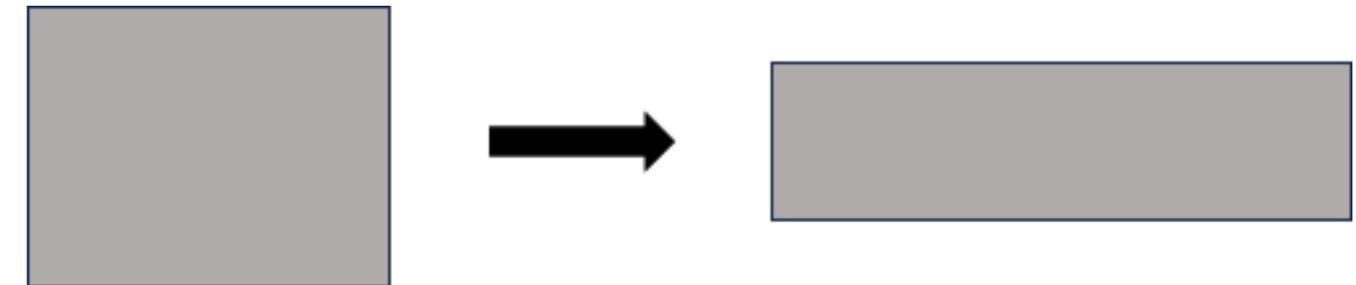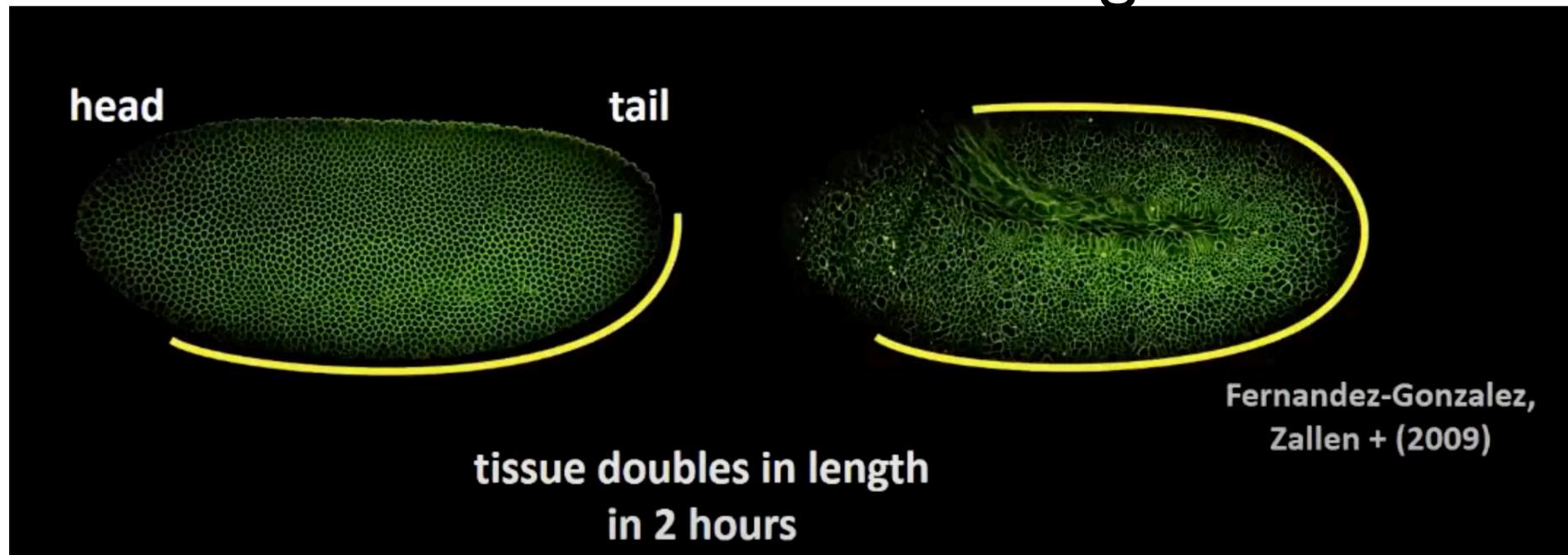
Different cells express different amounts of proteins to adjust their interactions

Epithelial Tissues during Development

Tah, Härtter, Crawford, Kiehart, Schmidt, Liu (2024)
Arzash, Tah, Liu, Manning (2024)
Arzash, Liu Manning

50 µm

0.00 min

- **Function**: tissue doubles in length in 2 hours at fixed area

head   tail

tissue doubles in length
in 2 hours

Fernandez-Gonzalez,
Zallen + (2009)
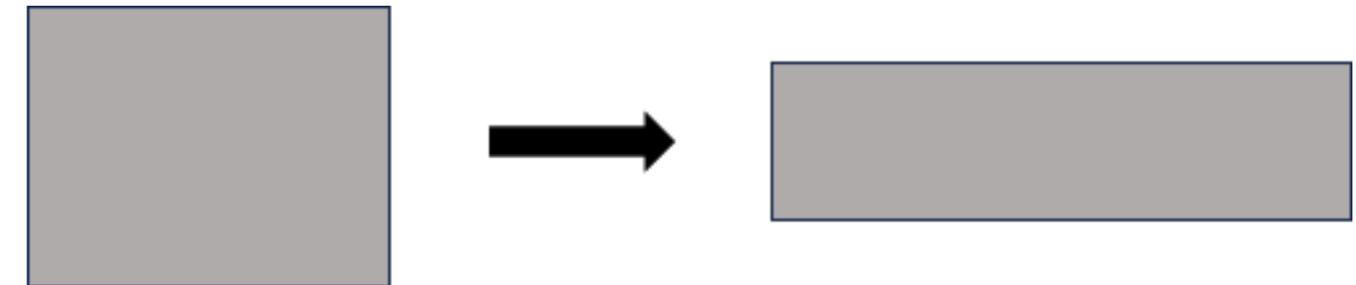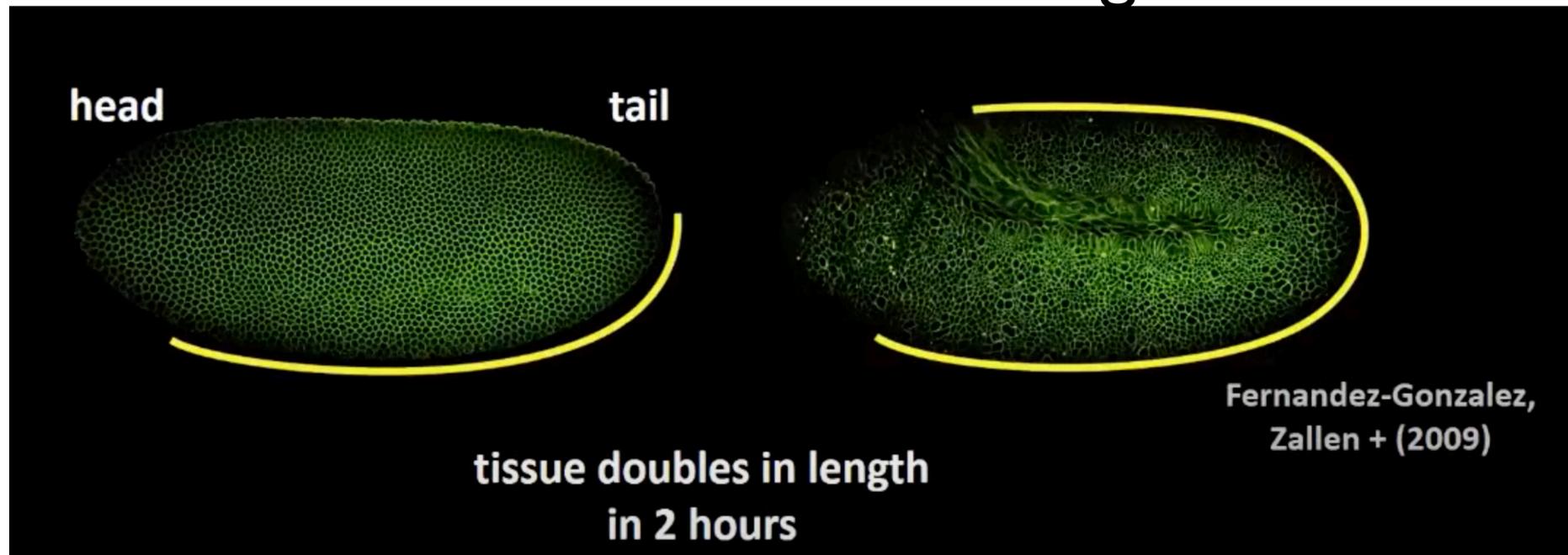
Different cells express different amounts of proteins to adjust their interactions

Tunable Vertex Model of 2D (Epithelial) Tissue

$$E = k_p \sum_{cells} (p_i - p_0)^2 + k_a \sum_{cells} (a_i - a_0)^2$$

Cell's optimal perimeter

actomyosin contractility
adhesion/cortical tension

Cell's optimal area

cell incompressibility
preferred cell height

Introduce junctional tensions as tunable DOF

Double optimization:
(1) adjust vertex positions to minimize E
(2) adjust junctional tensions to elongate tissue

Model I
$$E = \sum_{cells} E_i = \sum_{cells} \left[K_{A,i}(A_i - A_{0,i})^2 + K_{P,i}(P_i - P_{0,i})^2 \right] + \underbrace{\sum_{edges} T_{ij}\ell_{ij}}_{E_T}$$

Model II
$$E = \sum_{cells} E_i = \sum_{cells} \left[K_A(A_i - A_0)^2 \right] + \sum_{edges} T_{ij}\ell_{ij}$$

Arzash, Liu, Manning

Yes—by Evolution

- Evolution is great!
- But…
- It is very slow, requiring many generations

Yes—by Evolution

- Evolution is great!
- But…
- It is very slow, requiring many generations

Can tunable degrees of freedom be adjusted for desired collective response without a processor on time scales fast compared to evolution?

Decentralized Tuning via Local Rule (Don't Have to Know **Everything**)

Myosin-dependent junction remodelling controls planar cell intercalation and axis elongation

Claire Bertet, Lawrence Sulak & Thomas Lecuit
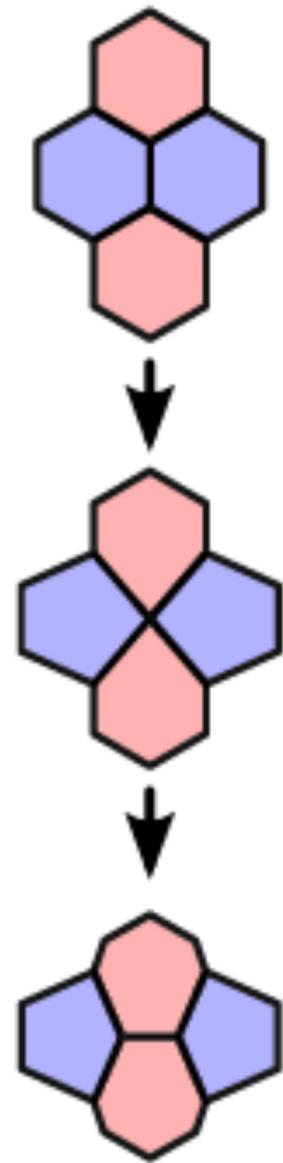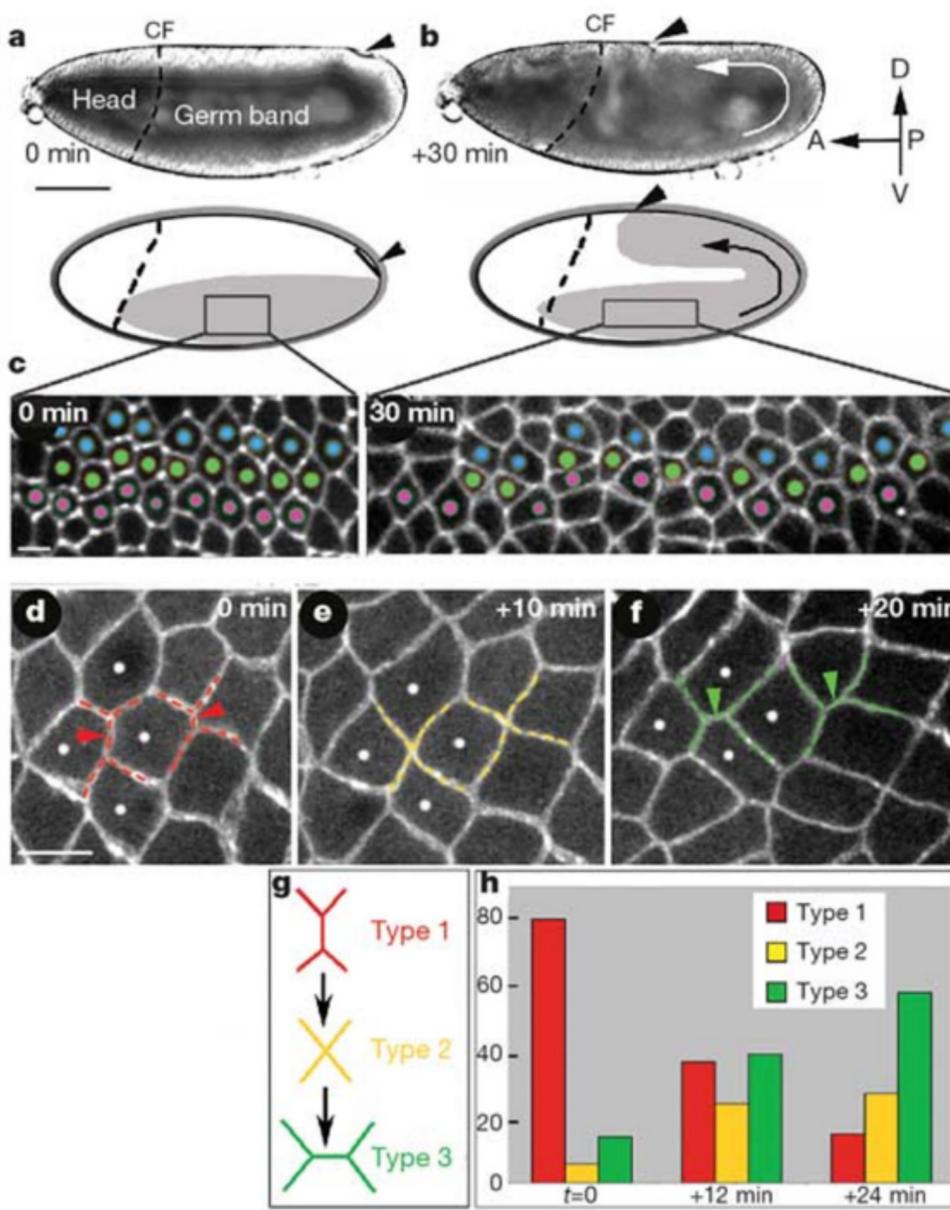
Myosin || is highly localized on vertical edges

The contractility of actomyosin (high tension) shrinks vertical edges

Results in these directed cell rearrangements that are necessary for tissue flow

Myosin Intensity Depends on Angle of Junction
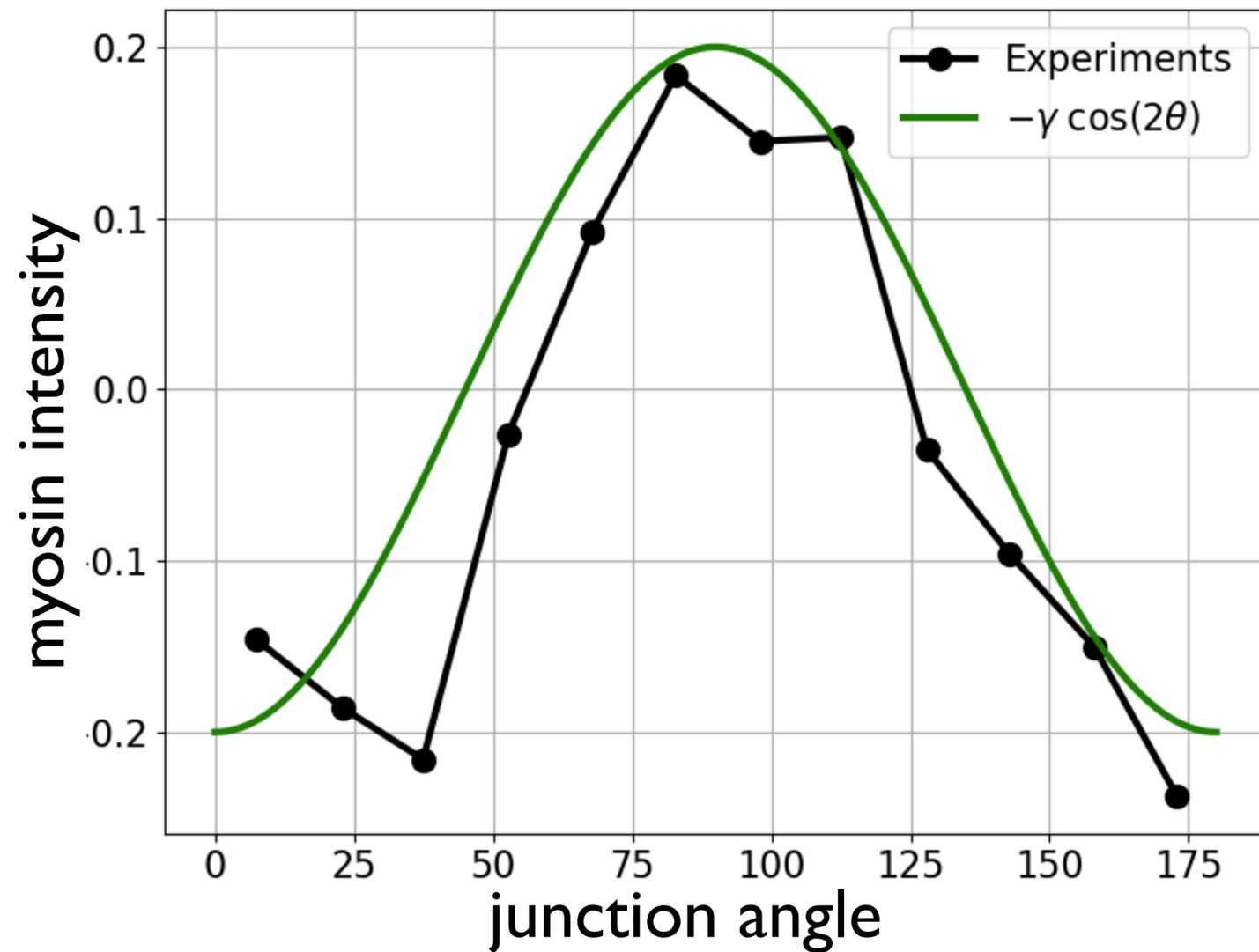
Blankenship et al., Dev. Cell (2006)

Local rule:

Lower vertex model energy cost of extension*

*directed aging: Pashine, Hexner, Liu, Nagel Sci Adv (2019)

$$\frac{dT_{ij}}{dt} \propto -T_{ij}\ell_{ij}\cos(2\theta)$$

Arzash, Liu, Manning, bioRxiv (2025)

Myosin Intensity Depends on Angle of Junction
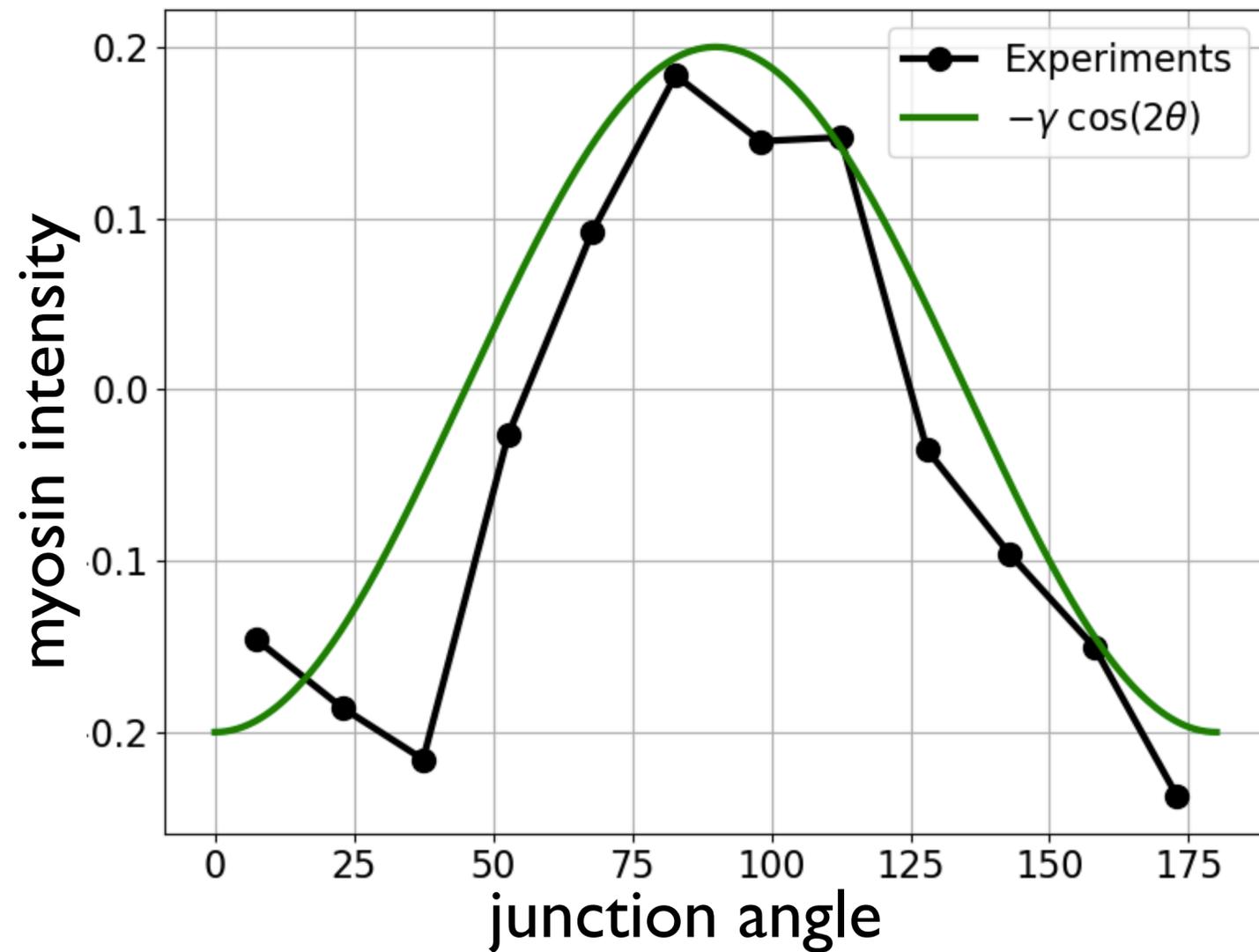
Blankenship et al., Dev. Cell (2006)

Local rule:

Lower vertex model energy cost of extension*

*directed aging: Pashine, Hexner, Liu, Nagel Sci Adv (2019)

$$\frac{dT_{ij}}{dt} \propto -T_{ij}\ell_{ij}\cos(2\theta)$$

tuning process requires heterogeneity!

Arzash, Liu, Manning, bioRxiv (2025)

Convergent Extension Driven by Local Rule
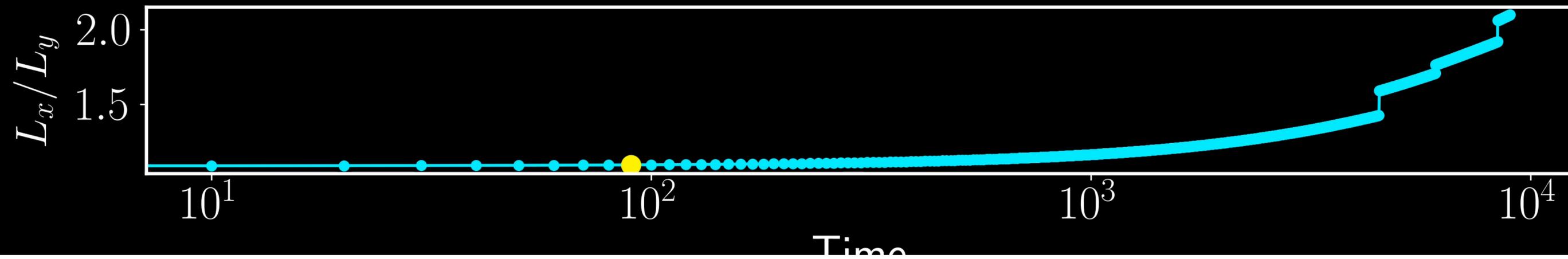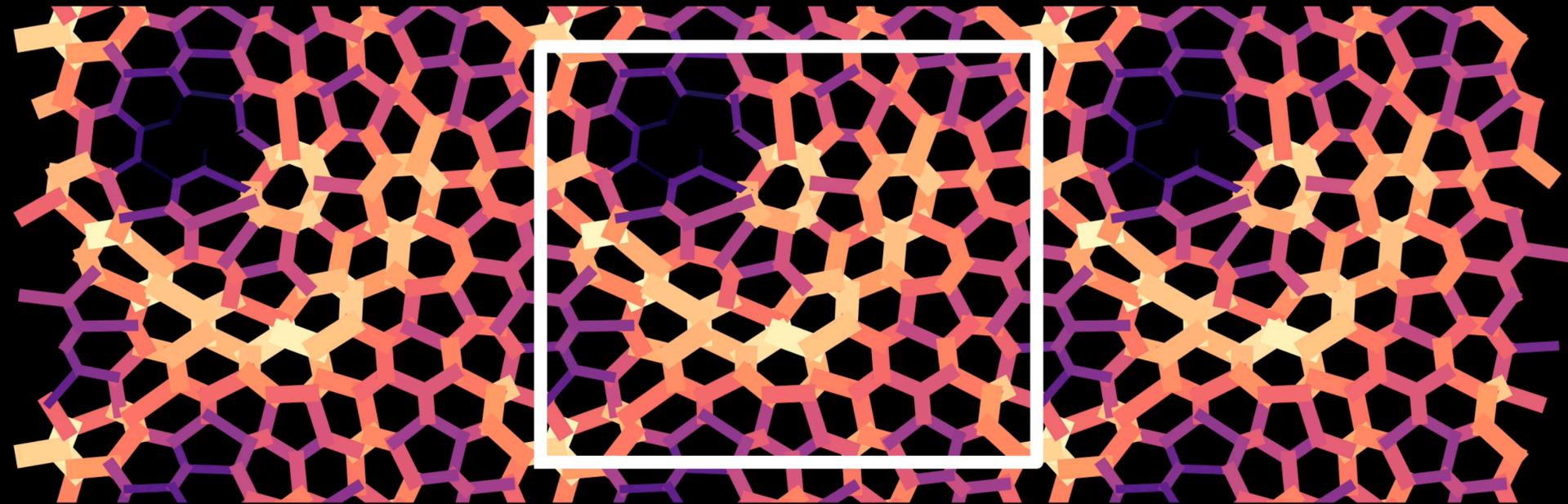
Convergent Extension Driven by Local Rule
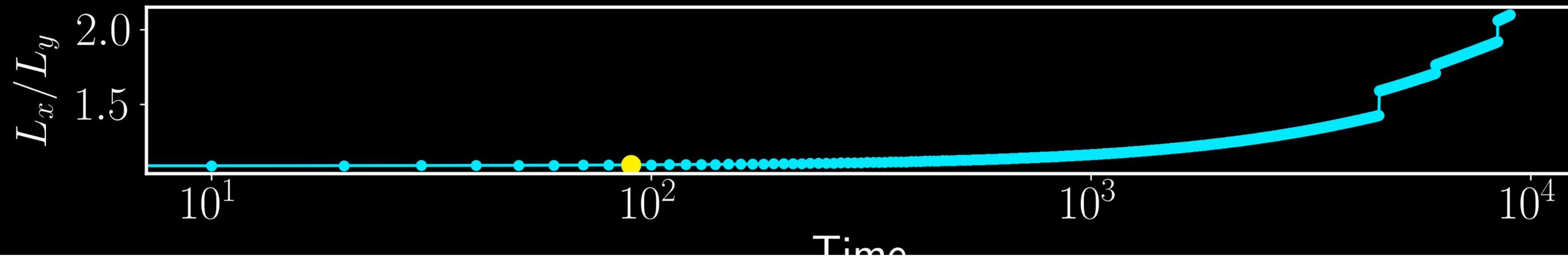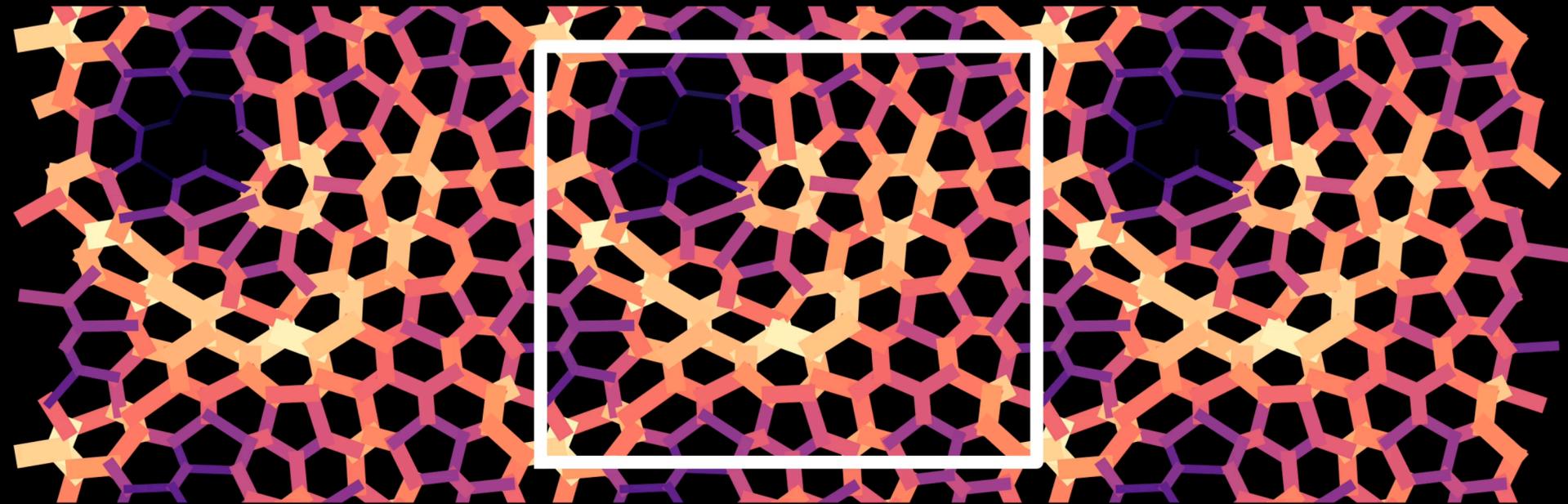
Convergent Extension Driven by Local Rule
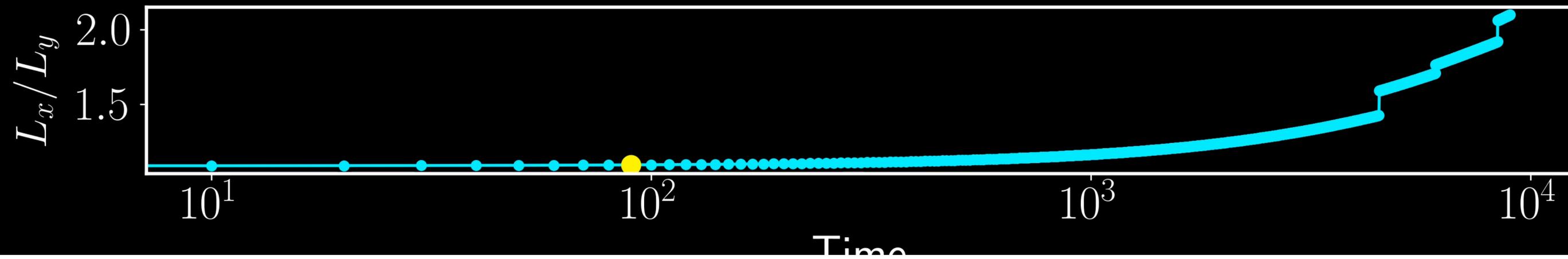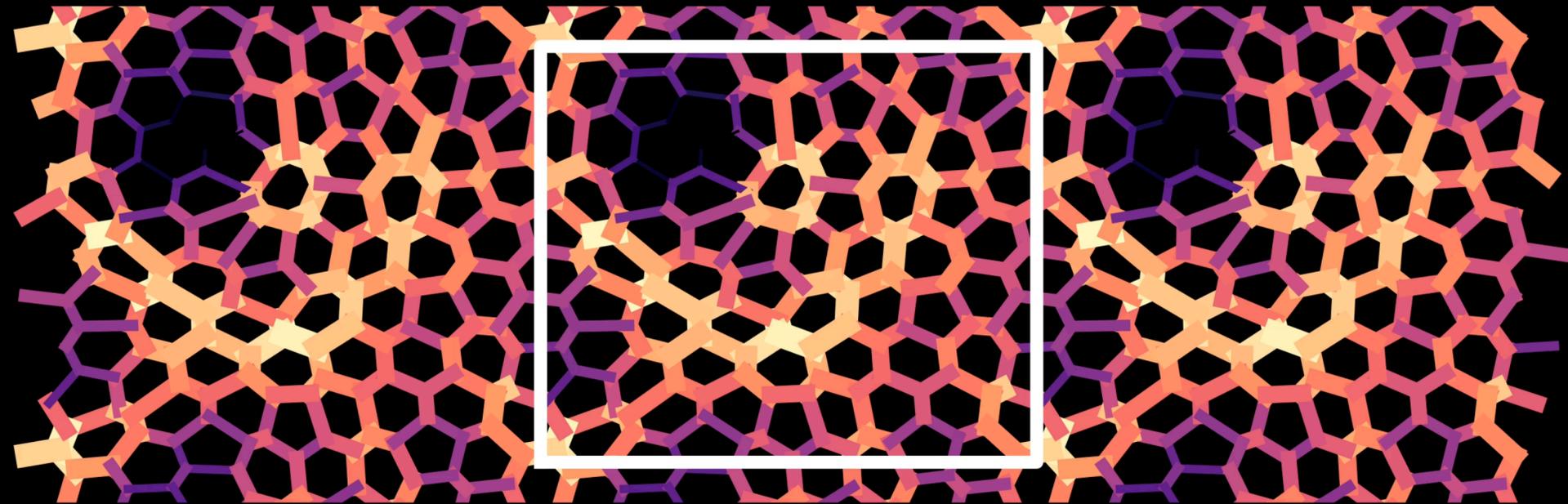
Myosin Intensity Depends on Angle of Junction
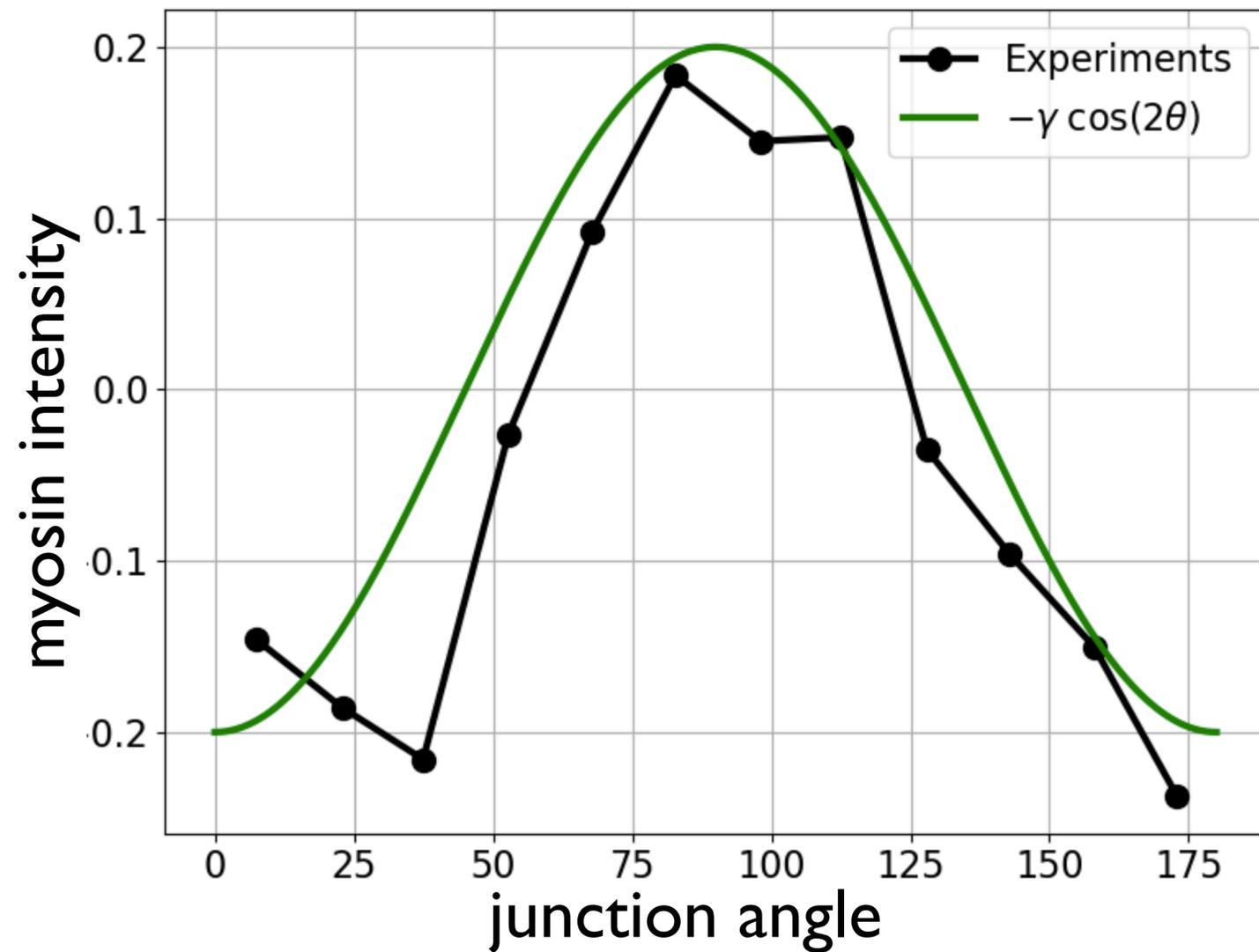
"O" Local rule:

$$\frac{dT_{ij}}{dt} = -\gamma T_{ij} \cos(2\theta_{ij})$$

"LO" Local rule:

$$\frac{dT_{ij}}{dt} = -\gamma T_{ij} \ell_{ij} \cos(2\theta_{ij})$$

Blankenship et al., Dev. Cell (2006)

Wang, et al. PNAS (2019)
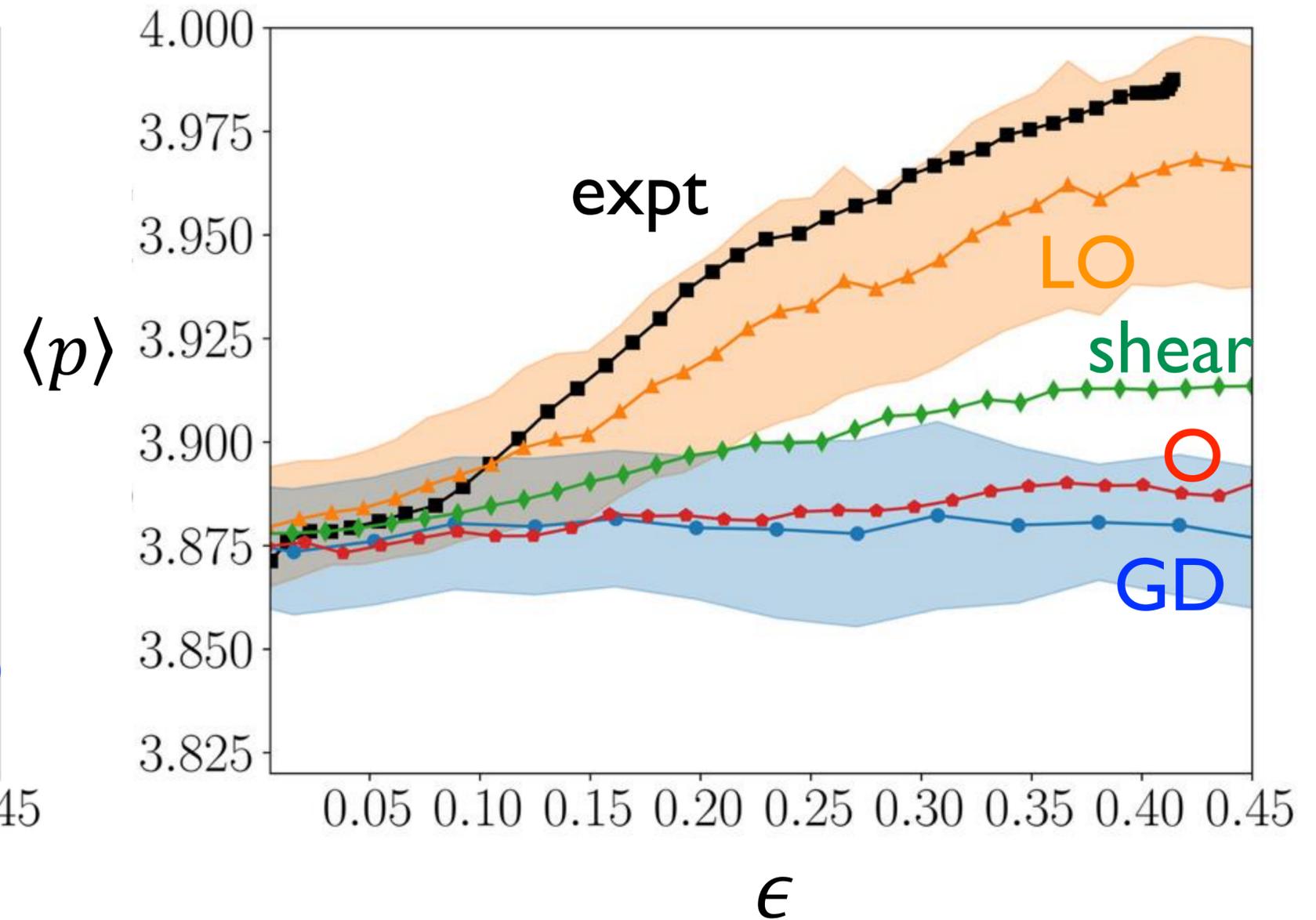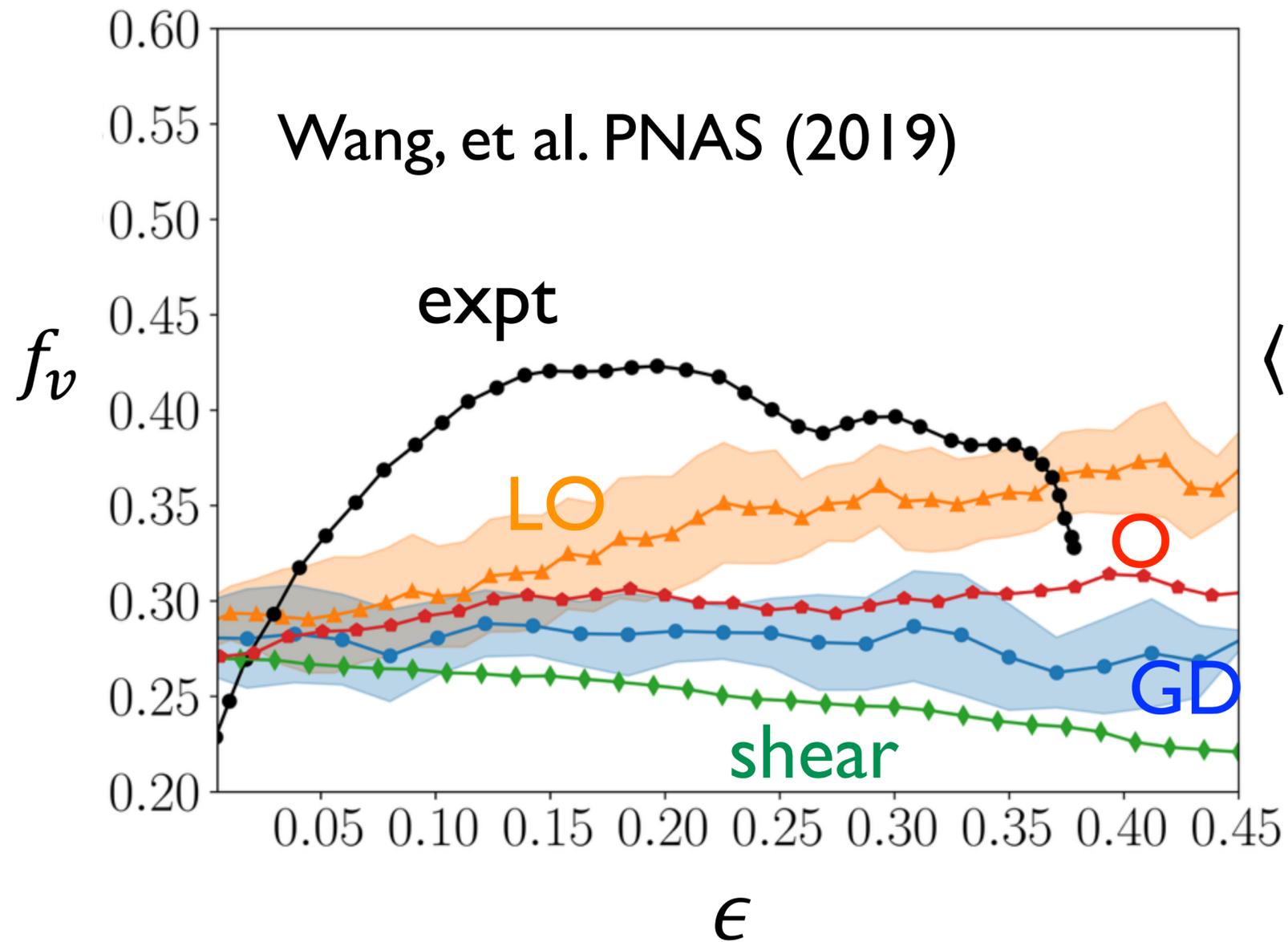
- Biologically-plausible local rule agrees better with experiments
- Can distinguish among ensembles of tuned solutions produced by different tuning processes to get insight into local rule!

Can satisfy constraints

Can't satisfy constraints
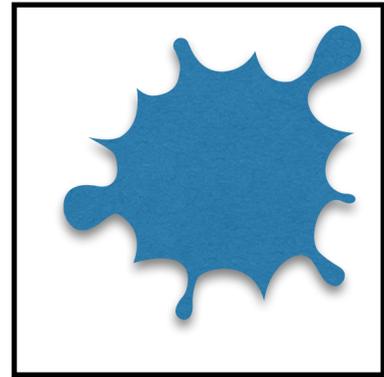
non-universal stuff

over-parameterized

under-parameterized

$$\frac{\#\ \text{constraints}}{\#\ \text{tunable DOF}} \ll 1$$
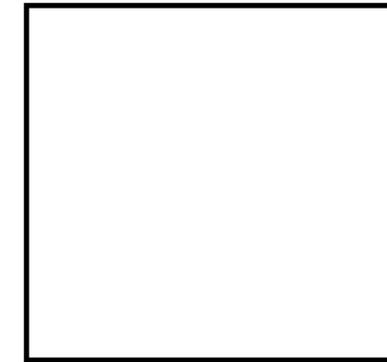
$$\frac{\#\ \text{constraints}}{\#\ \text{tunable DOF}} \sim 1$$

$$\frac{\#\ \text{constraints}}{\#\ \text{tunable DOF}} \gtrsim 1$$

- \# tunable DOFs is extensive in number of cells

- Easy/fast to find global minimum

- Generalizable: robust to stochasticity in gene expression, many mutations

- Many good solutions: ensemble of solutions is different for gradient descent/O local rule/LO local rule/external shear!
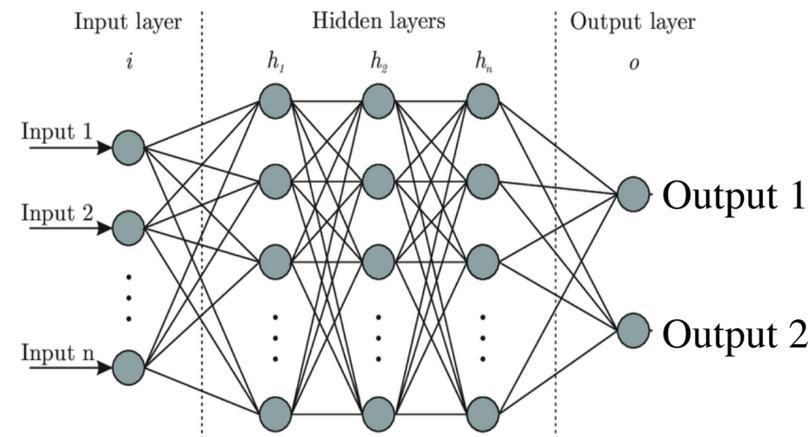
Another Reason to Love Local Rules (Decentralized Tuning)
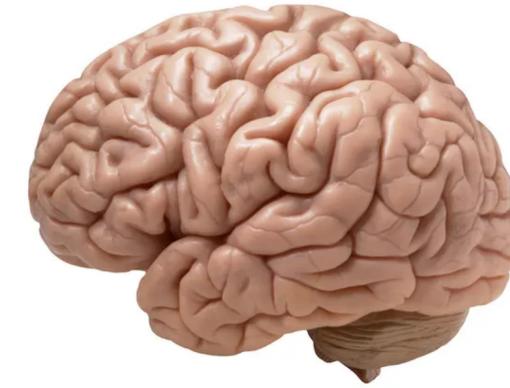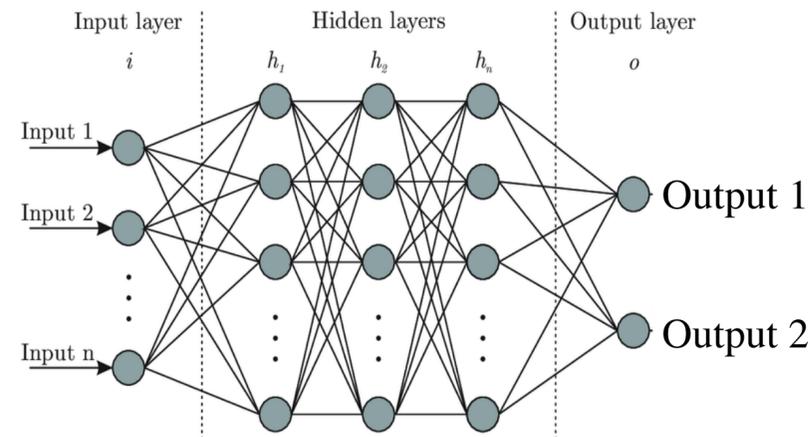
- Gradient descent on cost function requires knowing all network details

- Requires processor

- Neurons update via local rules (eg neurons fire together wire together
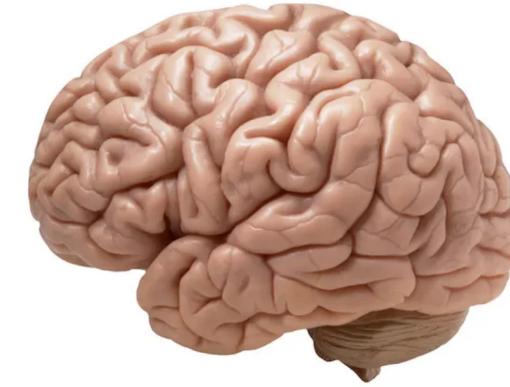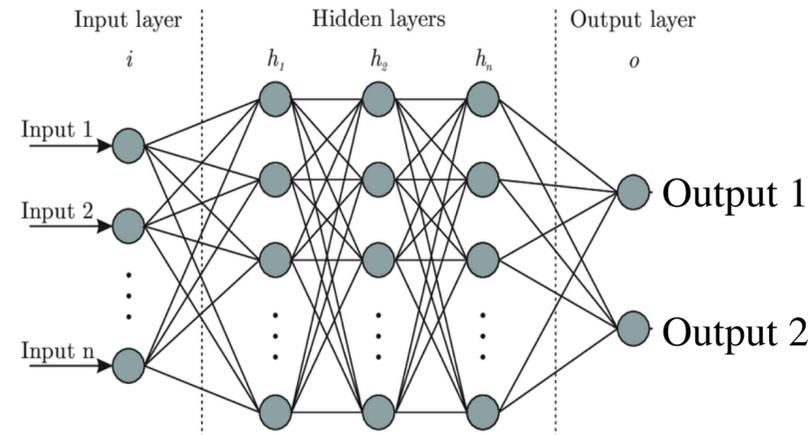
- Doesn't require processor

Why the Difference in Energy Efficiency?
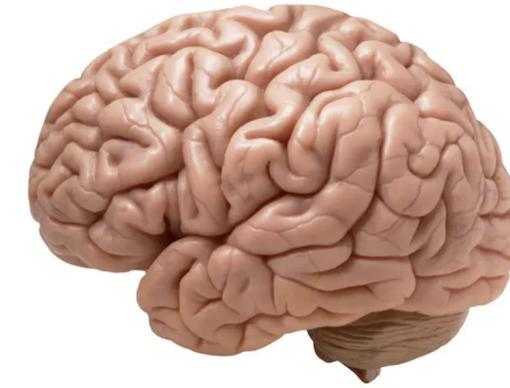
- Costs much energy
  - ChatGPT query for 100 words ~ 500 kJ
    Image generation ~10,000 kJ

- Digital

- von Neumann bottleneck/inference

- von Neumann bottleneck/training

- Energy efficient: adult human brain ~ 2000 kJ/day

- Analog

- In-memory compute

- In-memory learning

Differences in Learning

- Mainly feedforward
- Requires much data to train
- Digital/Precise/Fast
- Needs A/D conversion of analog data
- von Neumann bottleneck/inference
- von Neumann bottleneck/training
- Can be parallelized

- Highly recurrent
- Can require little data to train
- Analog/Imprecise, Noisy/Slow
- Natural for processing analog data
- In-memory compute
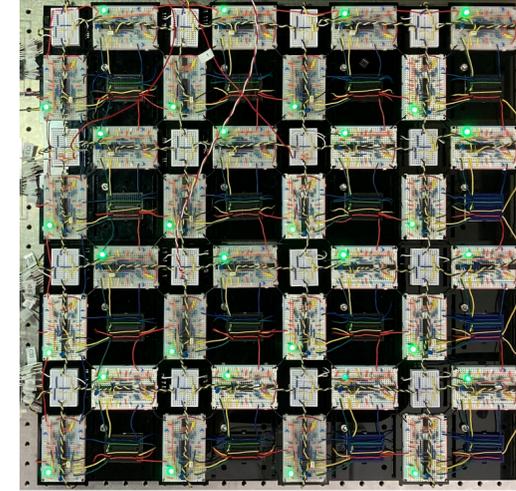- In-memory learning
- Decentralized/automatically parallelized

Contrastive Local Learning Networks
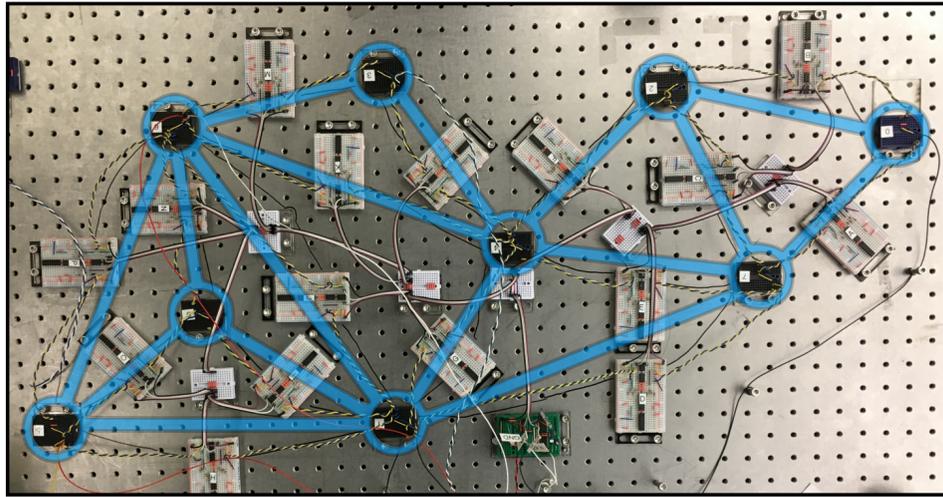
Gen 1: electrical networks of adjustable linear resistors
Dillavou/Stern/Liu/Durian PRApplied (2022)

Gen 1I: electrical networks of adjustable nonlinear resistors
Dillavou/Beyer/Stern/Liu/Miskin/Durian PNAS (2024)
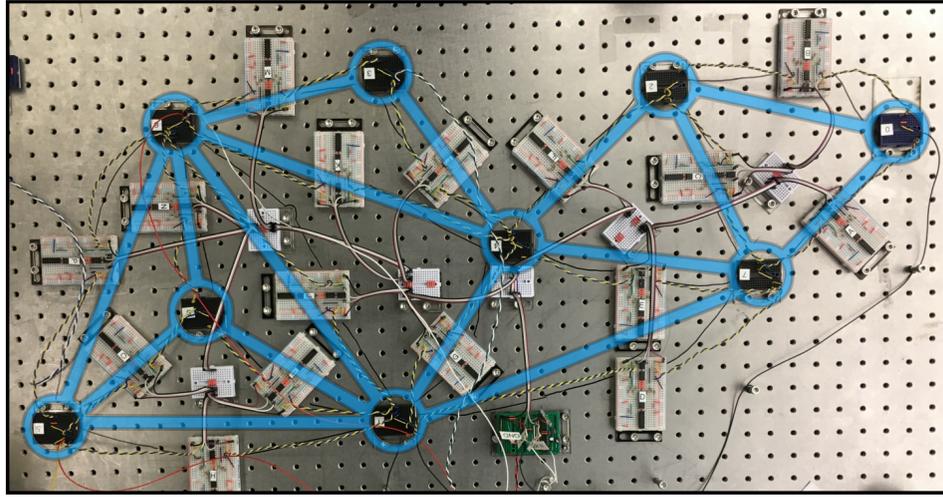
Stern, Hexner, Rocks, Liu PRX 2021

- Analog

- Perform gradient descent using local rule

- In-memory compute/learning
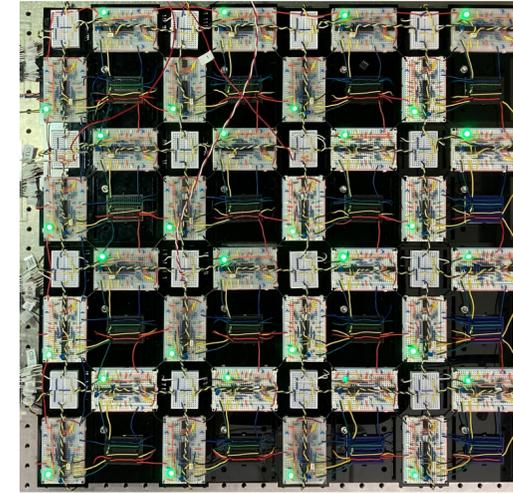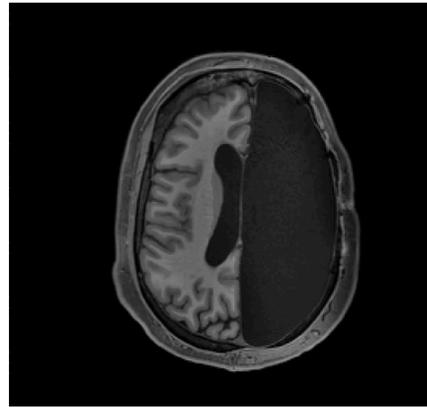
- Automatically parallelized

- As recurrent as desired

- Doesn't mimic brain!

- Physical relaxation performs inference automatically

- Physics harnesses local rule for supervised learning

Contrastive Local Learning Networks

Gen 1: electrical networks of
adjustable linear resistors
Dillavou/Stern/Liu/Durian PRApplied (2022)

Gen 1I: electrical networks of adjustable
nonlinear resistors
Dillavou/Beyer/Stern/Liu/Miskin/Durian PNAS (2024)

- **Linear supervised learning**
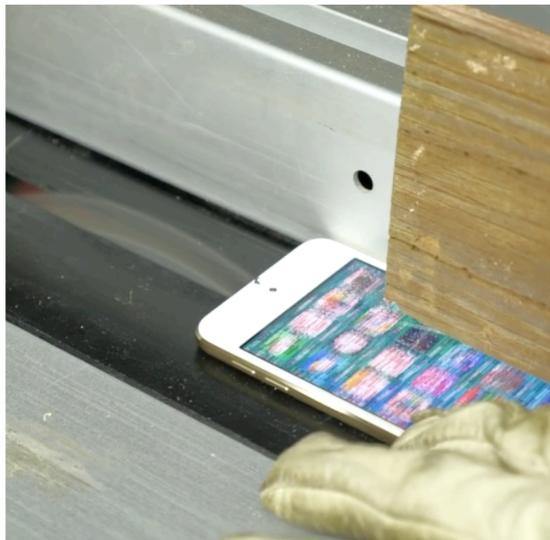
  – Linear regression

  – Linear classification

- **Nonlinear supervised learning**

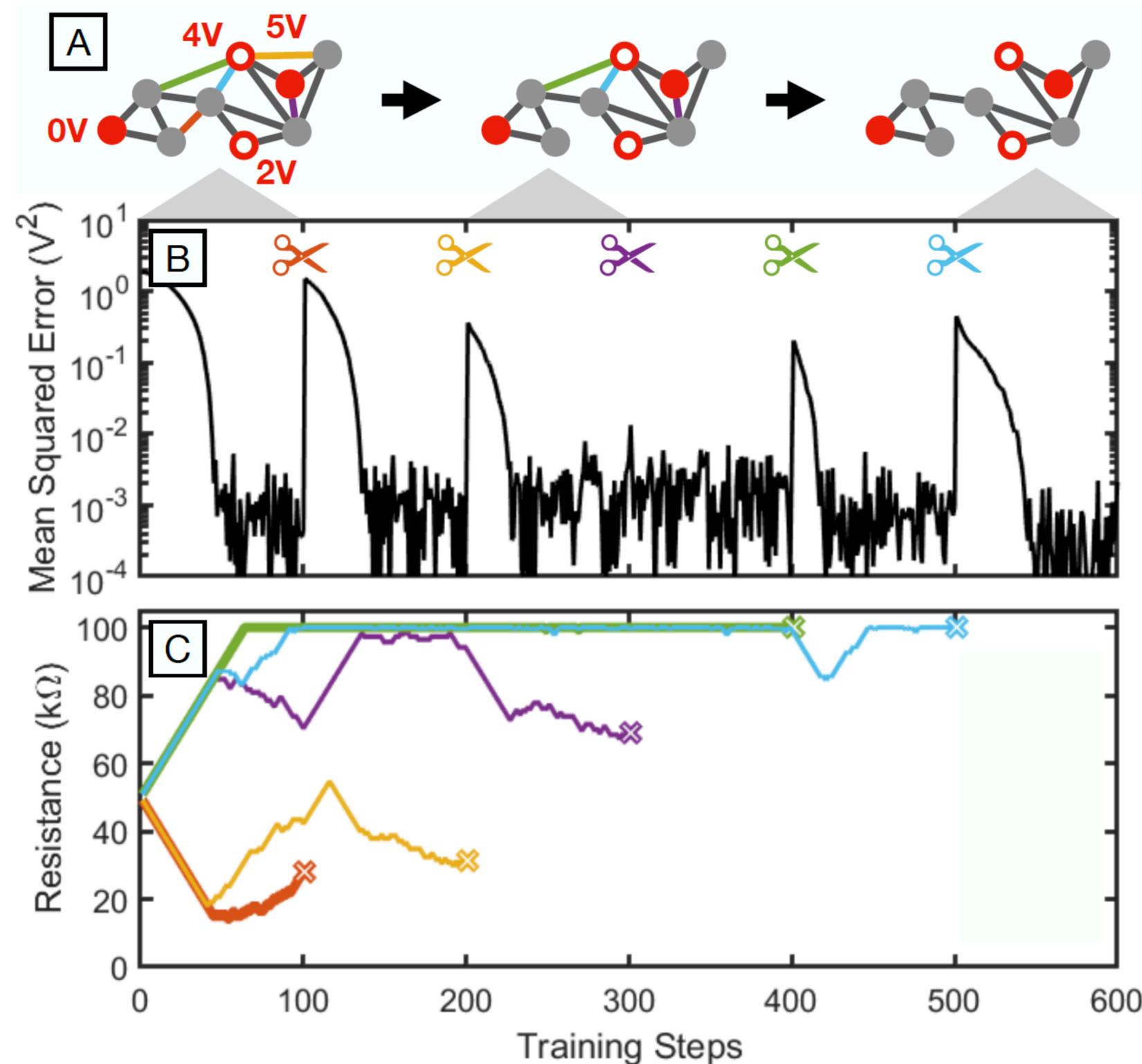 – Nonlinear regression

  – Nonlinear classification

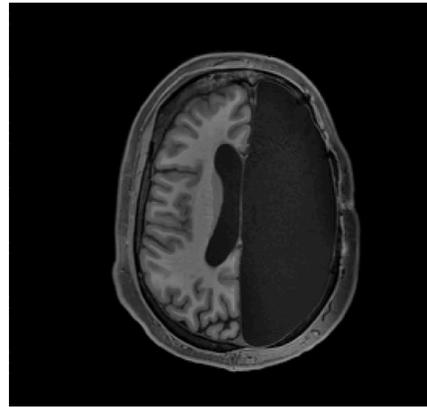- Brains incredibly robust to damage
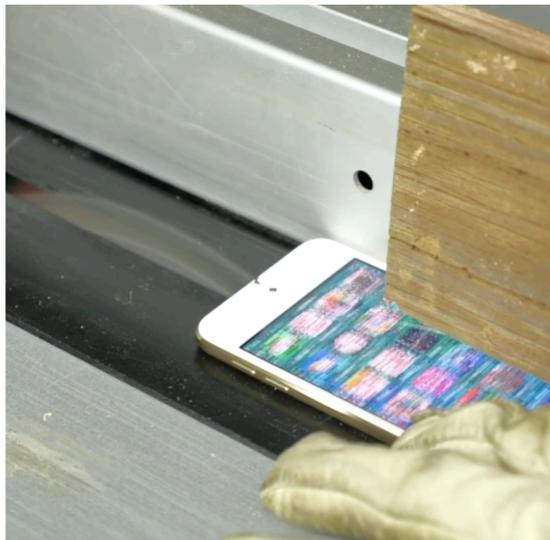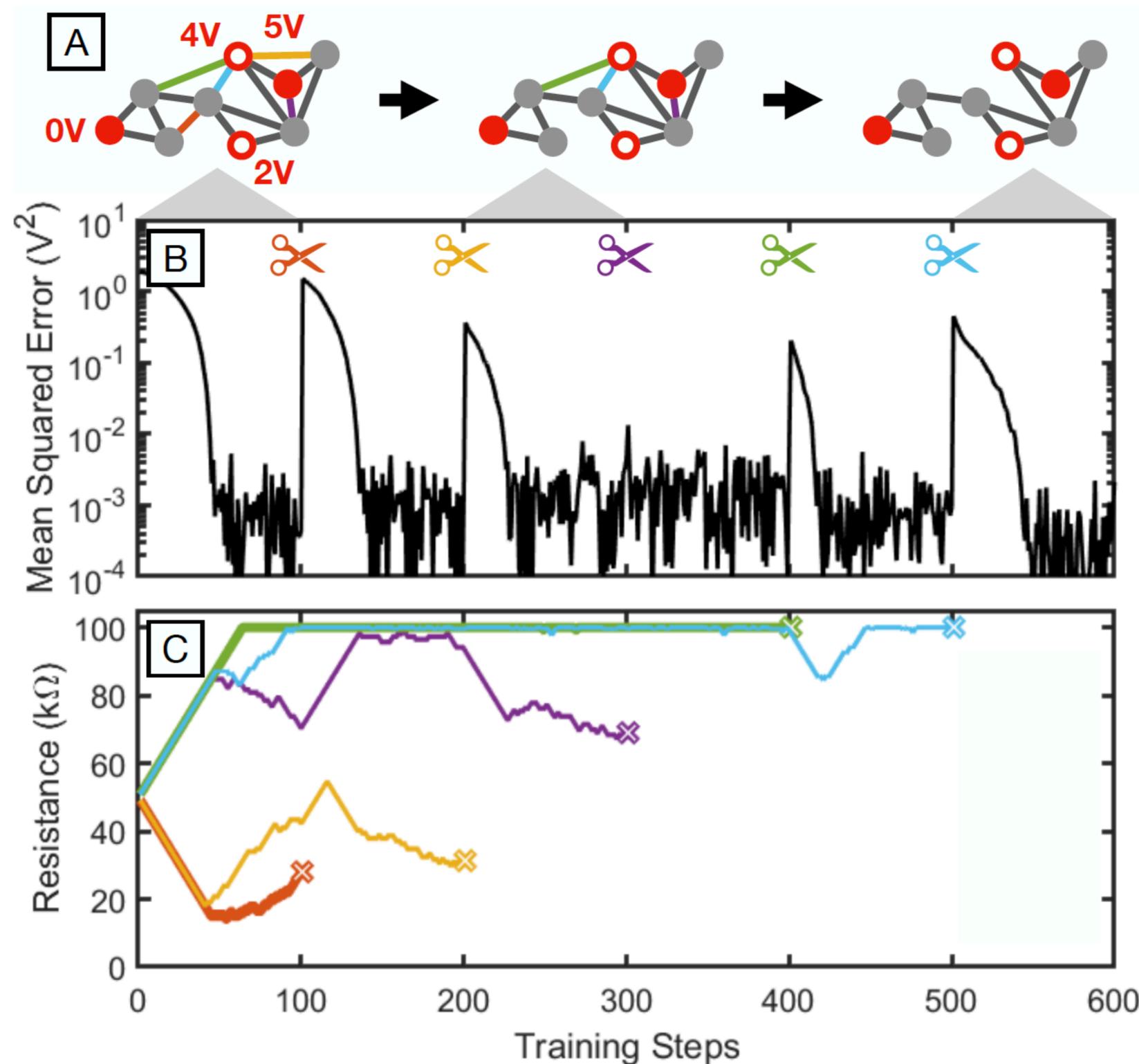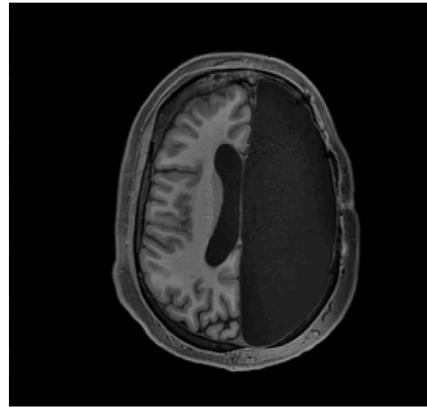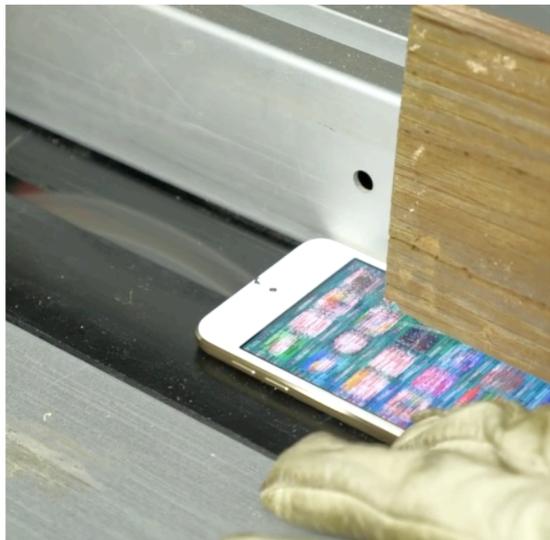
- processors aren't

- our networks are

To Scale Up, Need Robustness to Defective Edges

- Brains incredibly robust to damage

- processors aren't
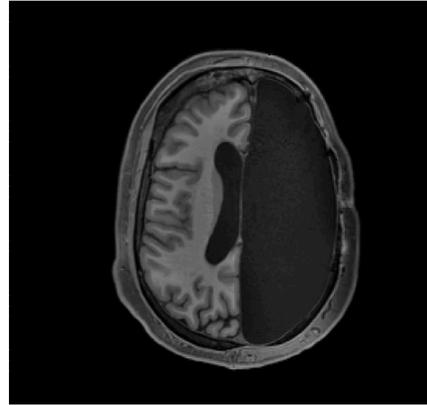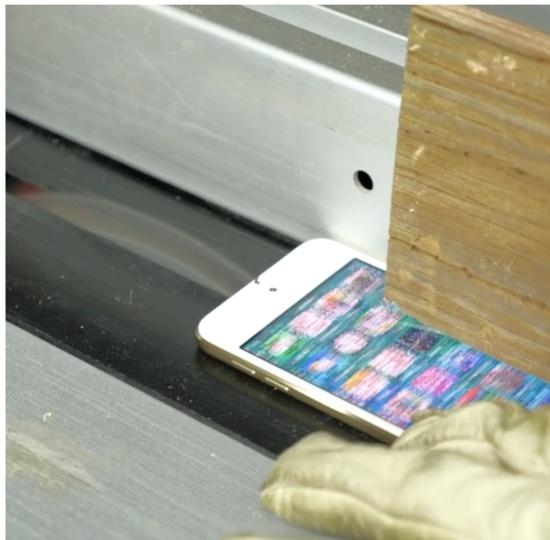
- our networks are

Dillavou, Stern, Liu, Durian, PR Applied (2022)

- Brains incredibly robust to damage

- processors aren't

- our networks are

- Brains incredibly robust to damage

- processors aren't

- our networks are
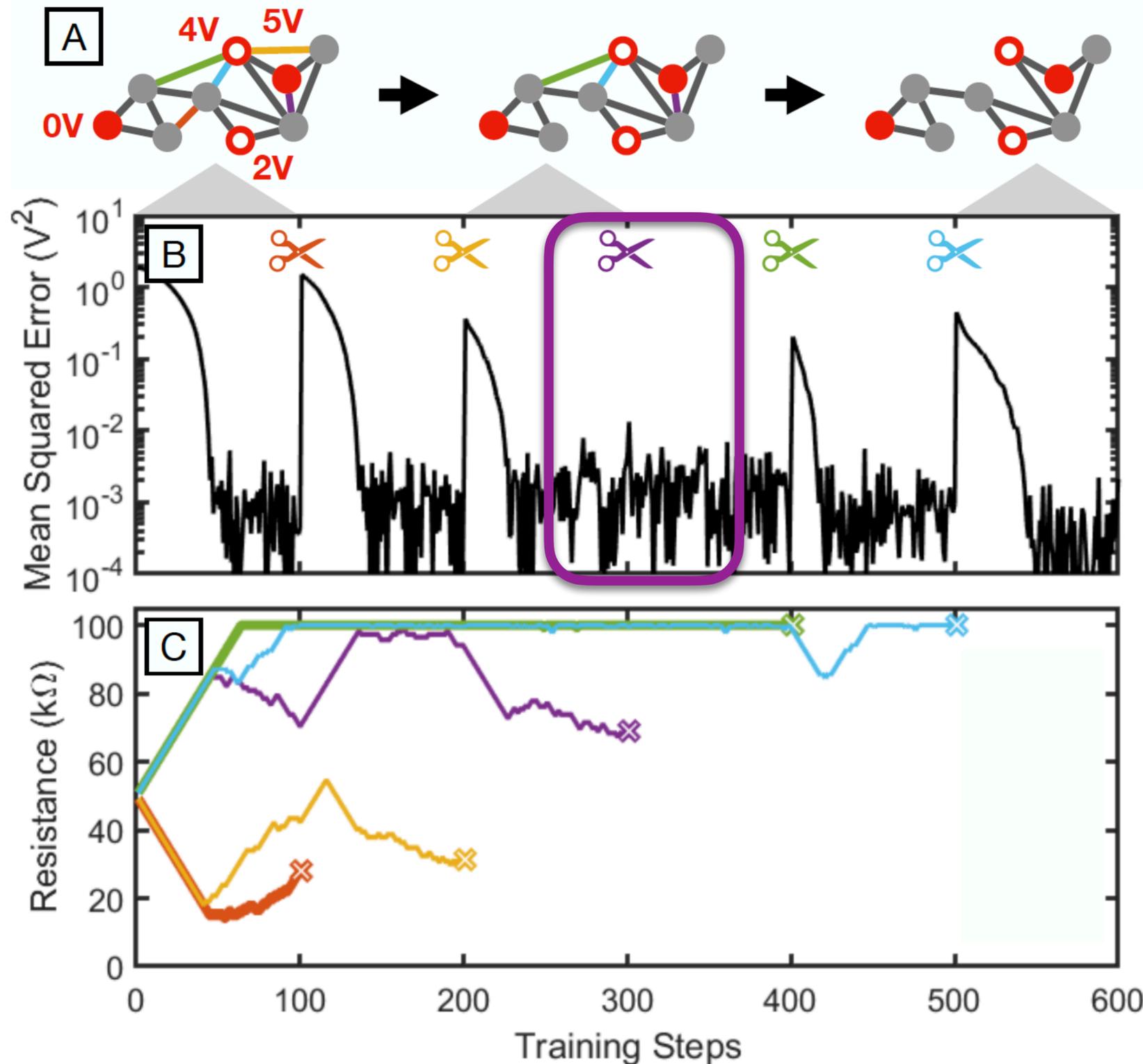
System is over-parameterized! Many different solutions to same task

Scaling Up

- Robust to damage so manufacturable

- Parameter changes are calculated in parallel by every edge

- Current ~10 pJ/parameter/inference

- Already comparable to ~1 pJ/parameter/inference on most energy-efficient Qualcomm AI chip

- Next step: printed circuit boards/chips for networks with ~100-200 edges (parameters)

- 3rd-gen design (Miskin) microfabrication of 100 edges on chip

  - 10 fJ/parameter/inference
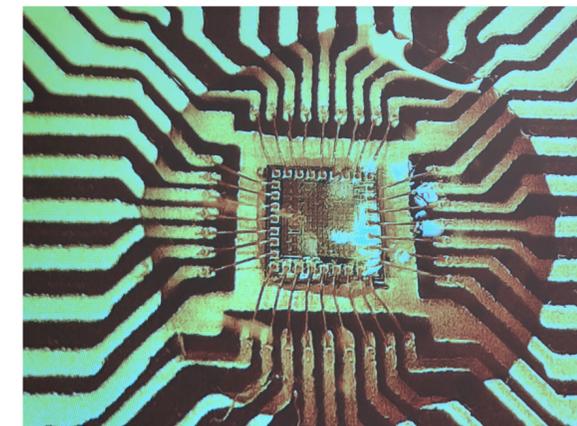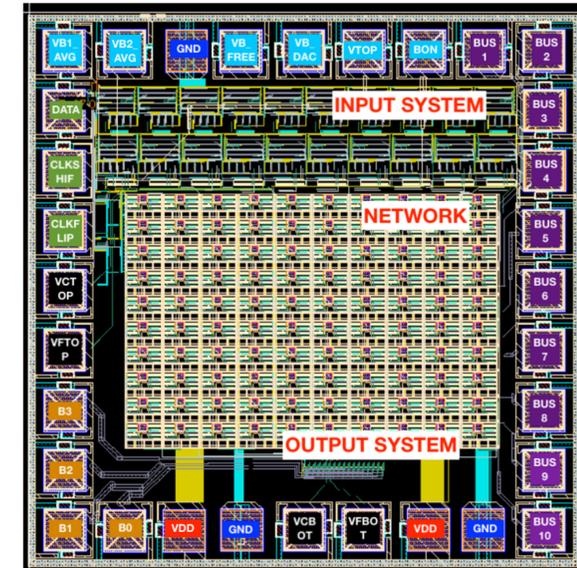
Why Lump These Systems Together?

- Proteins

- Epithelial tissue during convergent extension

- Contrastive Local Learning networks

- Allosteric proteins (Yue Shang, Adam Frim, Sid Nagel)

- Actin cortex (Haina Wang, Marco Galvani Cunha, John Crocker)

- Tumors (Haina Wang, John Crocker, Dennis Discher)

- Mitotic spindle (Emre Alca, Reza Farhadifar, Mike Shelley)

They share a common theoretical advantage

- Replace detailed parts list with simple tunable models to study emergence
- Study how detailed parts list gives tunability

Why Lump These Systems Together?

- Proteins

- Epithelial tissue during convergent extension

- Contrastive Local Learning networks

- Actin cortex (Haina Wang, Marco Galvani Cunha, John Crocker)

- Tumors (Haina Wang, John Crocker, Dennis Discher)

- Mitotic spindle (Emre Alca, Reza Farhadifar, Mike Shelley)

They share interesting common features

- Overparameterization
  - Easy/fast to find good solutions
  - Robustness to damage
  - Many good solutions

Tunable Matter

- Proteins
- Epithelial tissue during convergent extension
- Contrastive Local Learning networks
- Actin cortex (Haina Wang, Marco Galvani Cunha, John Crocker)
- Tumors (Haina Wang, John Crocker, Dennis Discher)
- Mitotic spindle (Emre Alca, Reza Farhadifar, Mike Shelley)

Are biological systems generically overparameterized for function?

Heterogeneity is both cause and consequence of tuning

Tunable matter is new class of condensed matter requiring new unifying frameworks

Challenge for condensed matter physics!

Thanks to

Sadjad
Arzash

Menachem
Stern

Sam
Dillavou

Lisa
Manning

Doug
Durian

Marc
Miskin