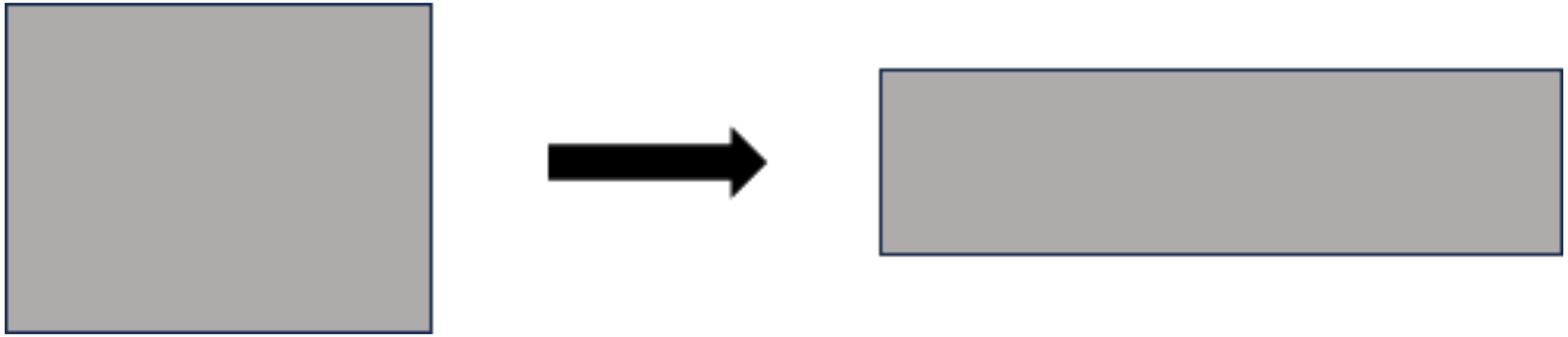
Back to Vertex Model: Convergent Extension

- During convergent extension, tissue doubles in length in 2 hours at fixed area



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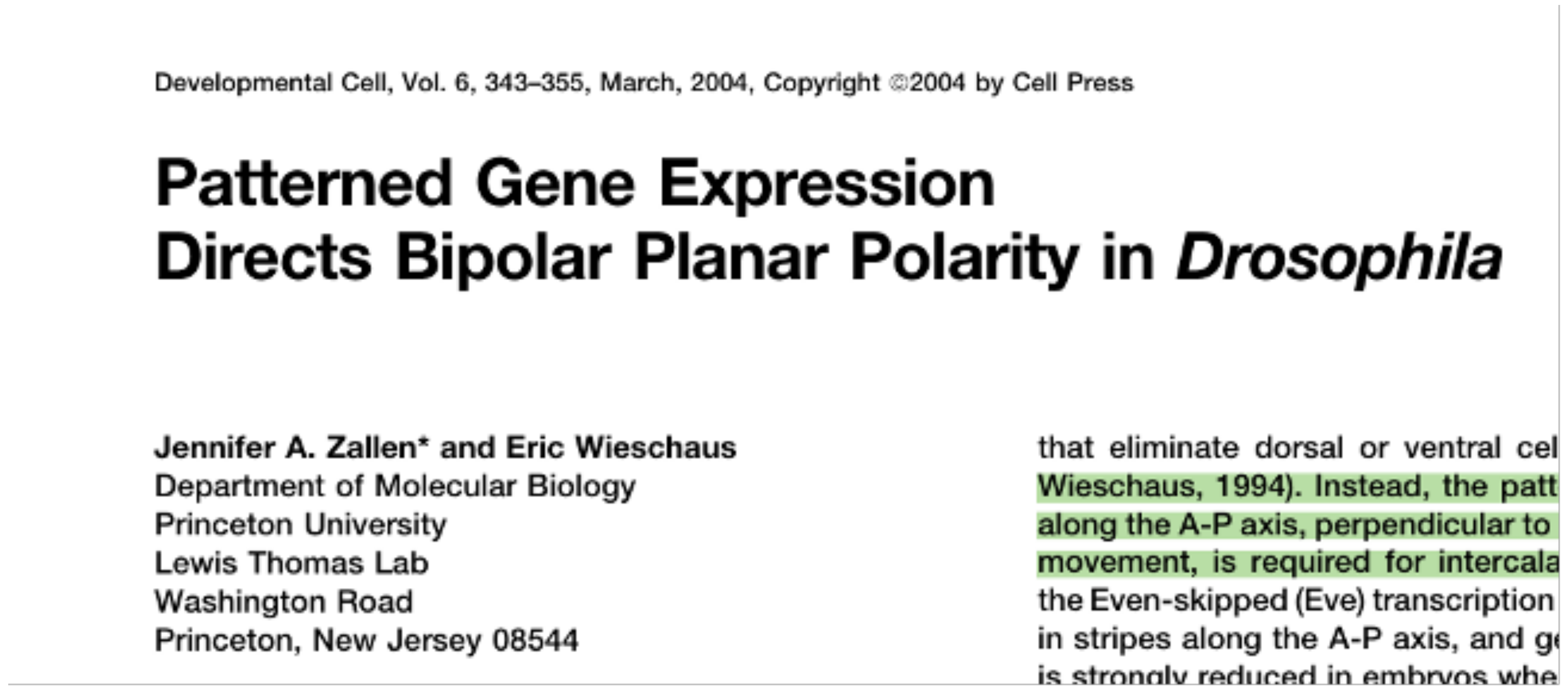
Sadjad Arzash, Lisa Manning

GO TO SLIDES

Myosin Polarization Drives Convergent Extension

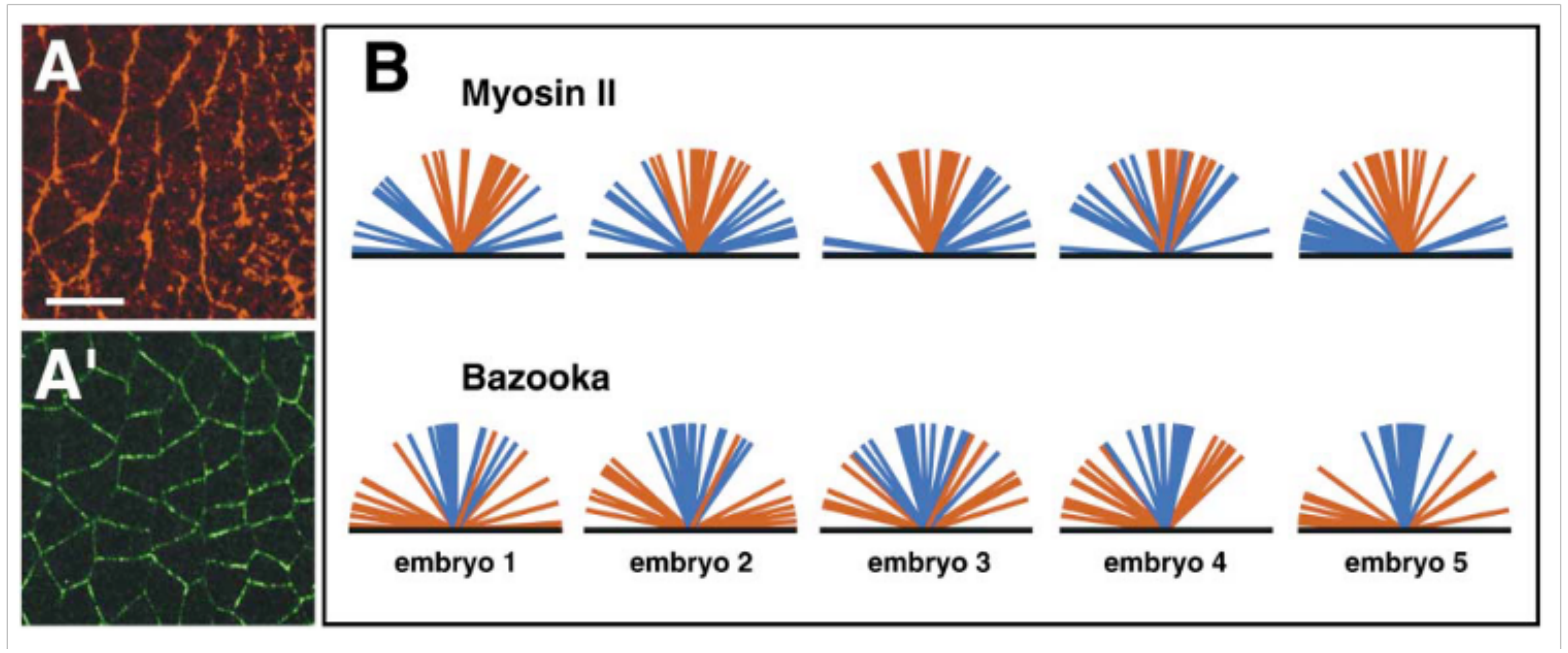


Developmental Cell, Vol. 6, 343–355, March, 2004, Copyright ©2004 by Cell Press

Patterned Gene Expression Directs Bipolar Planar Polarity in *Drosophila*

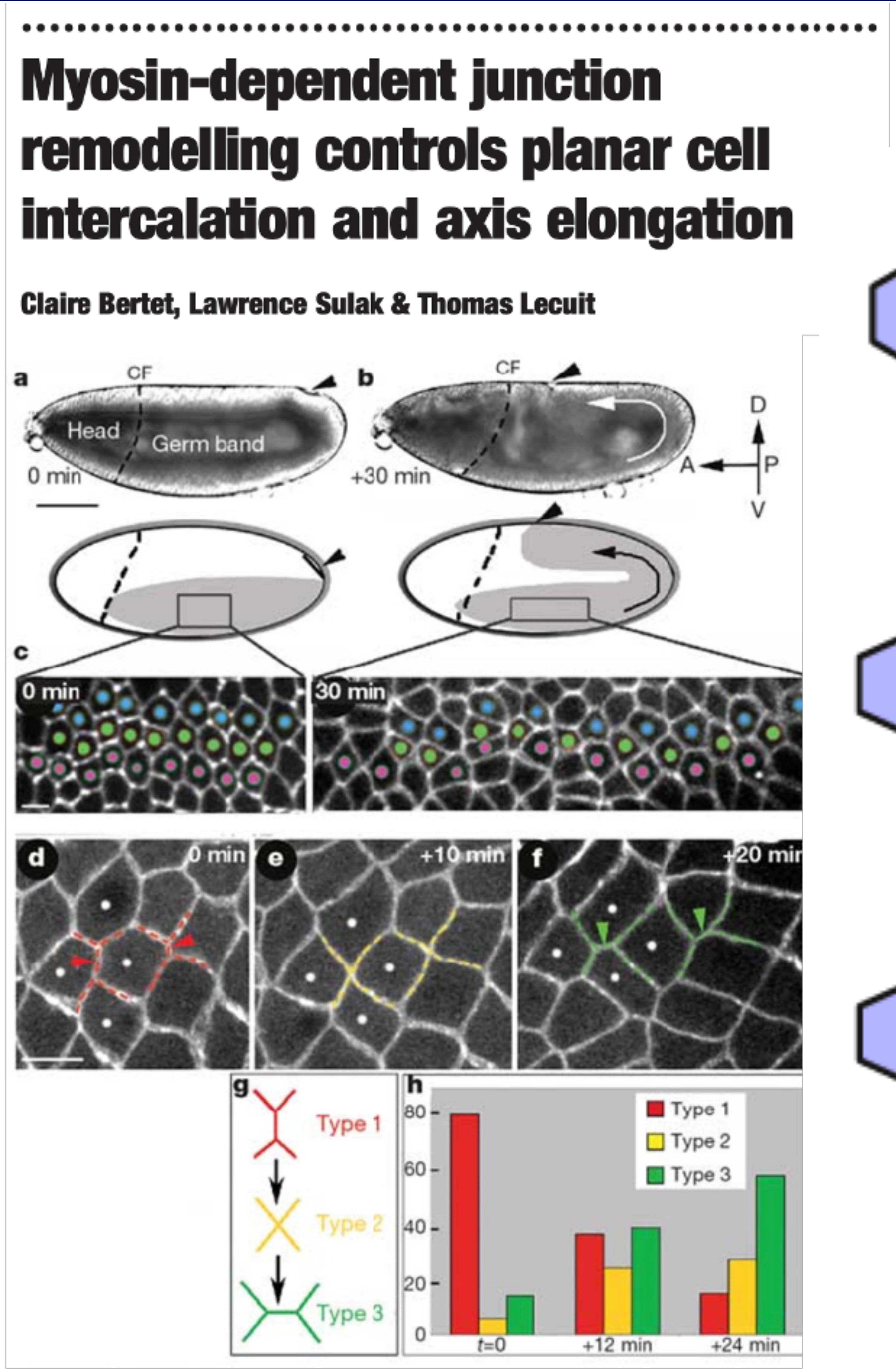
Jennifer A. Zallen* and Eric Wieschaus
Department of Molecular Biology
Princeton University
Lewis Thomas Lab
Washington Road
Princeton, New Jersey 08544

that eliminate dorsal or ventral cel
Wieschaus, 1994). Instead, the patt
along the A-P axis, perpendicular to
movement, is required for intercala
the Even-skipped (Eve) transcription
in stripes along the A-P axis, and g
is strongly reduced in embryos whe



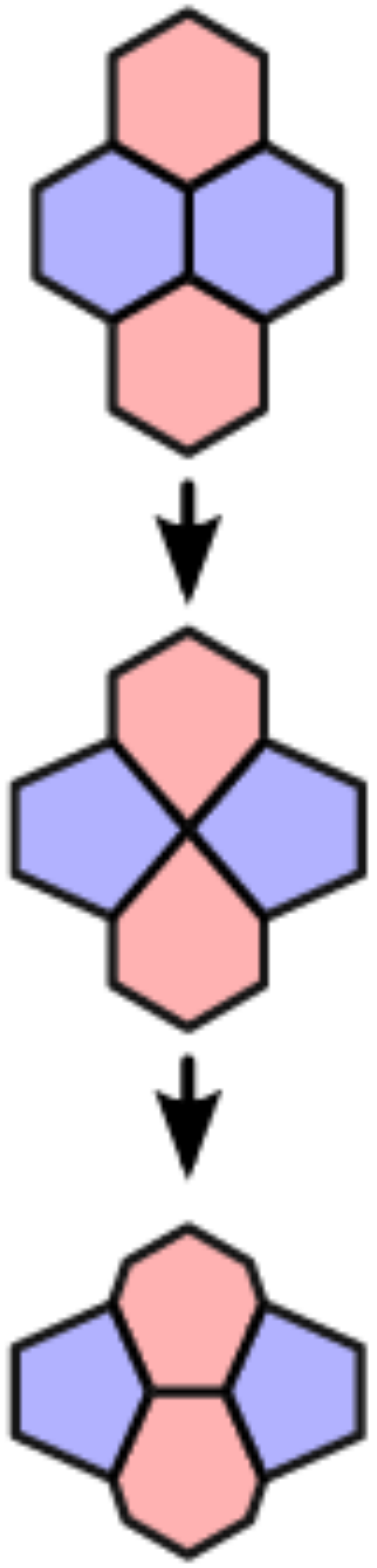
Myosin || is highly localized on vertical edges at the onset of convergent extension

Myosin Drives Directed T1 events



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

Introduce Edge Tensions as Parameters

- Vertex model with edge tensions

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

$$\frac{dT_{ij}}{dt} = -\gamma \, T_{ij} \underbrace{\left(\frac{\ell_{ij,x}^2 - \ell_{ij,y}^2}{\ell_{ij}} \right)}_{\propto \ \cos 2\theta}$$

local rule

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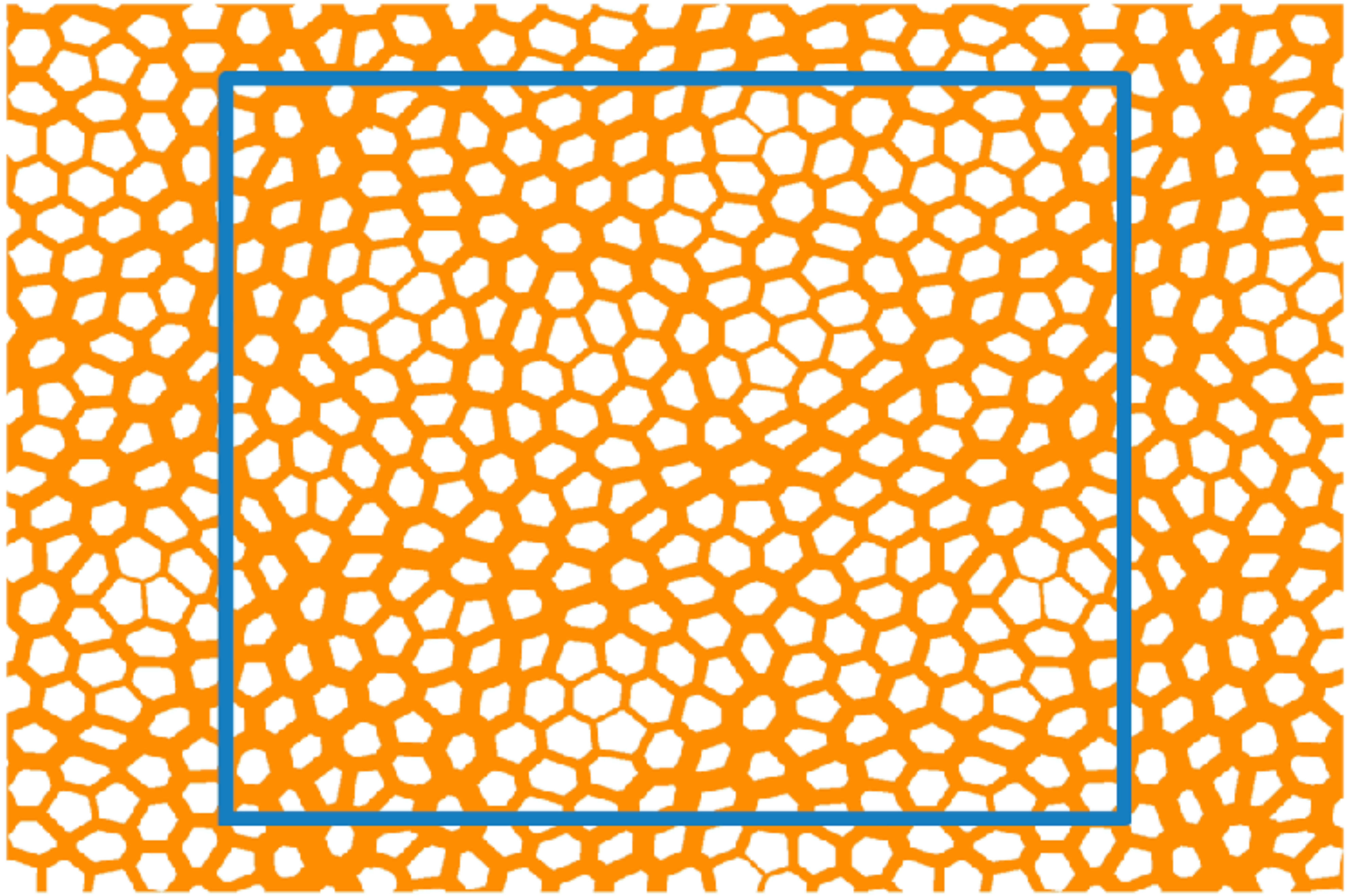
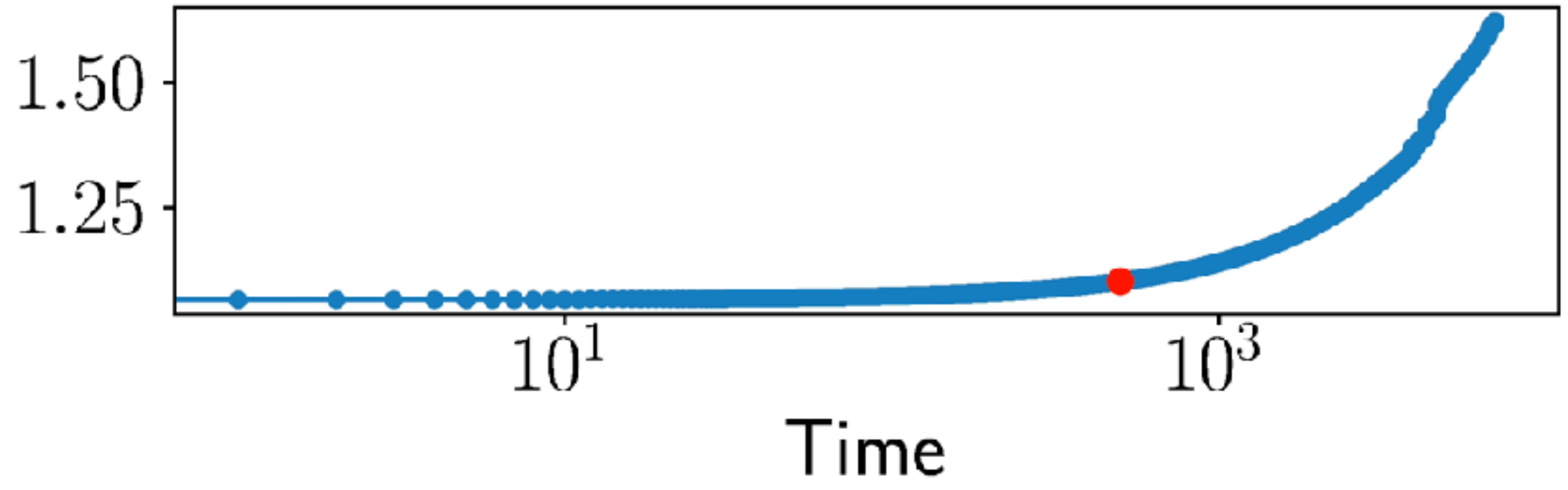
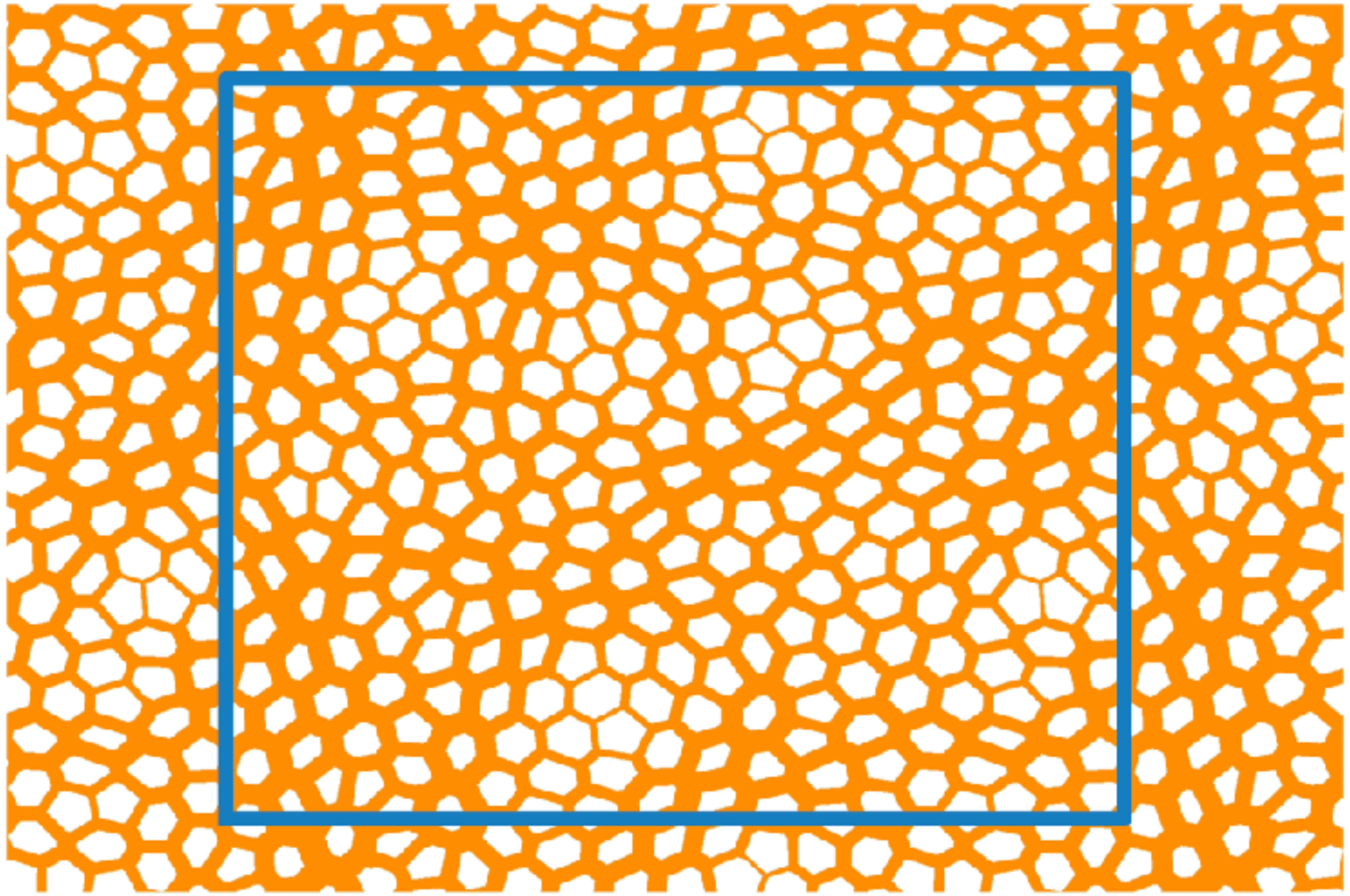
Convergent Extension Driven by Edge Tensions



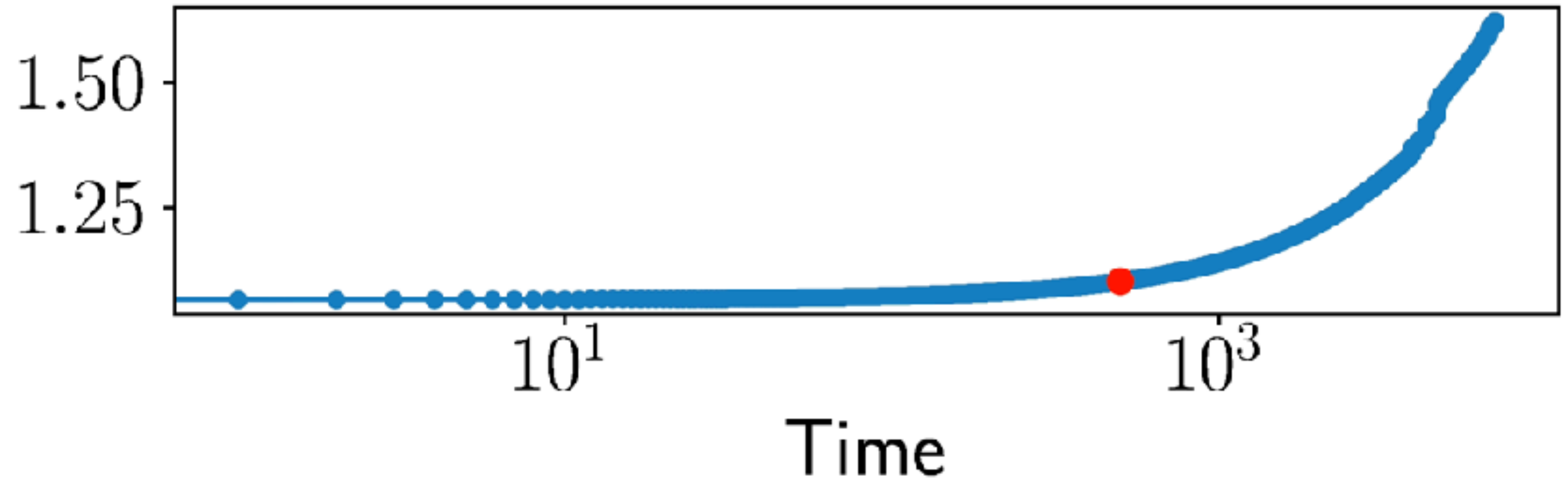
Aspect ratio



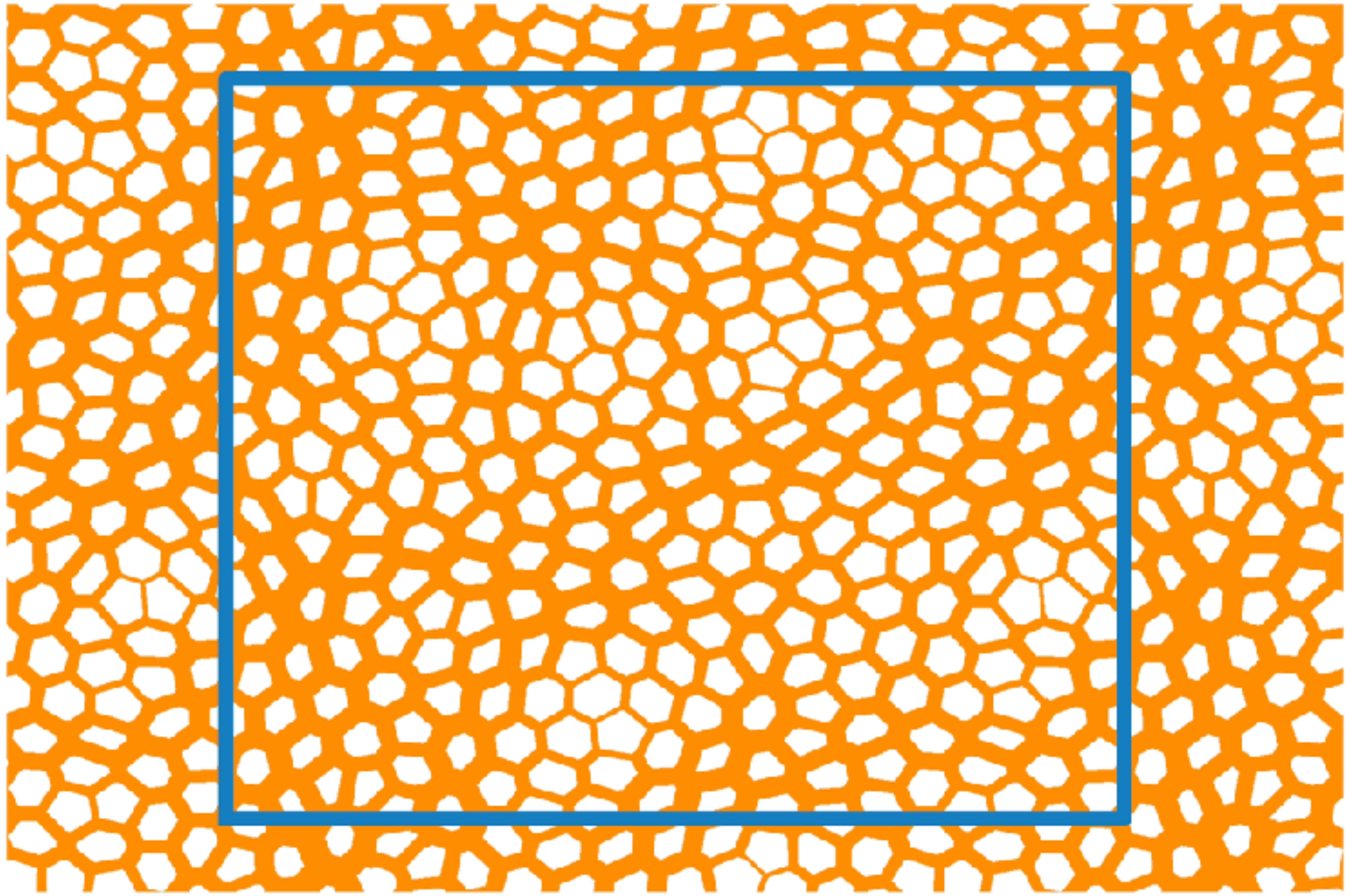
Convergent Extension Driven by Edge Tensions



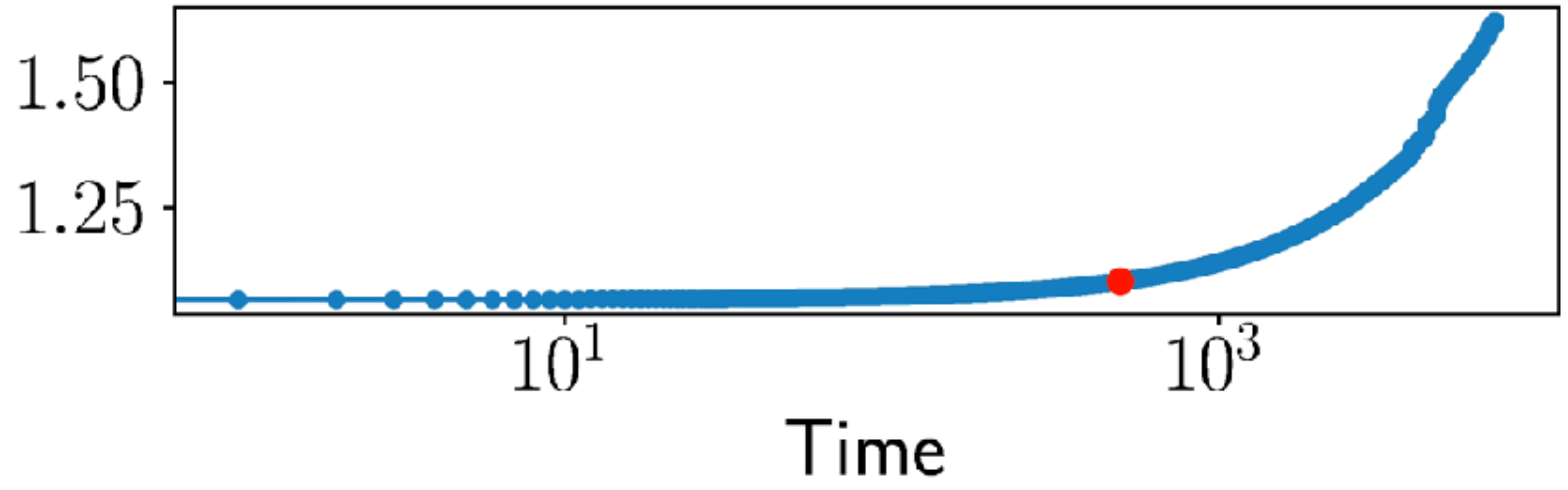
Aspect ratio



Convergent Extension Driven by Edge Tensions

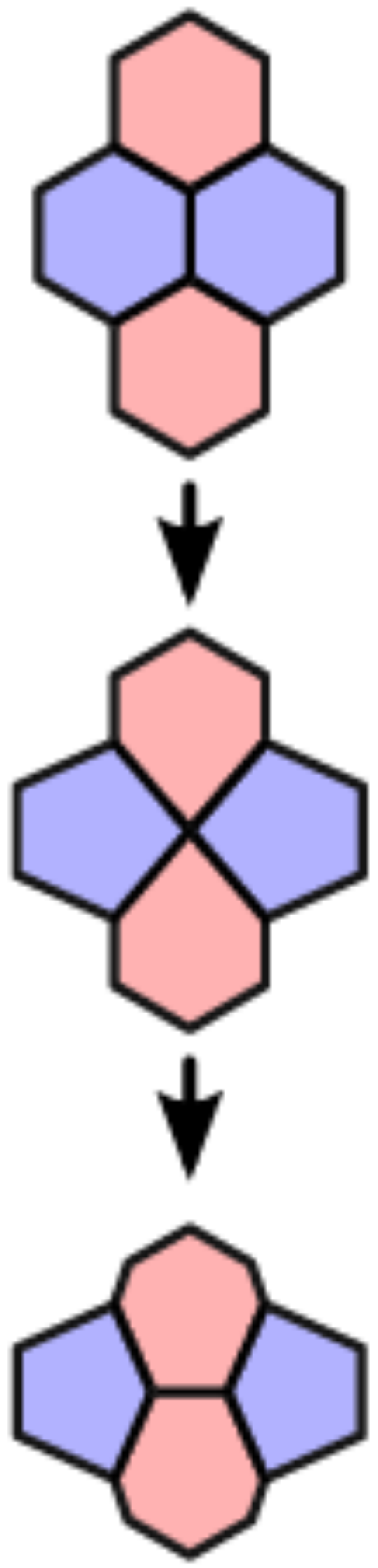


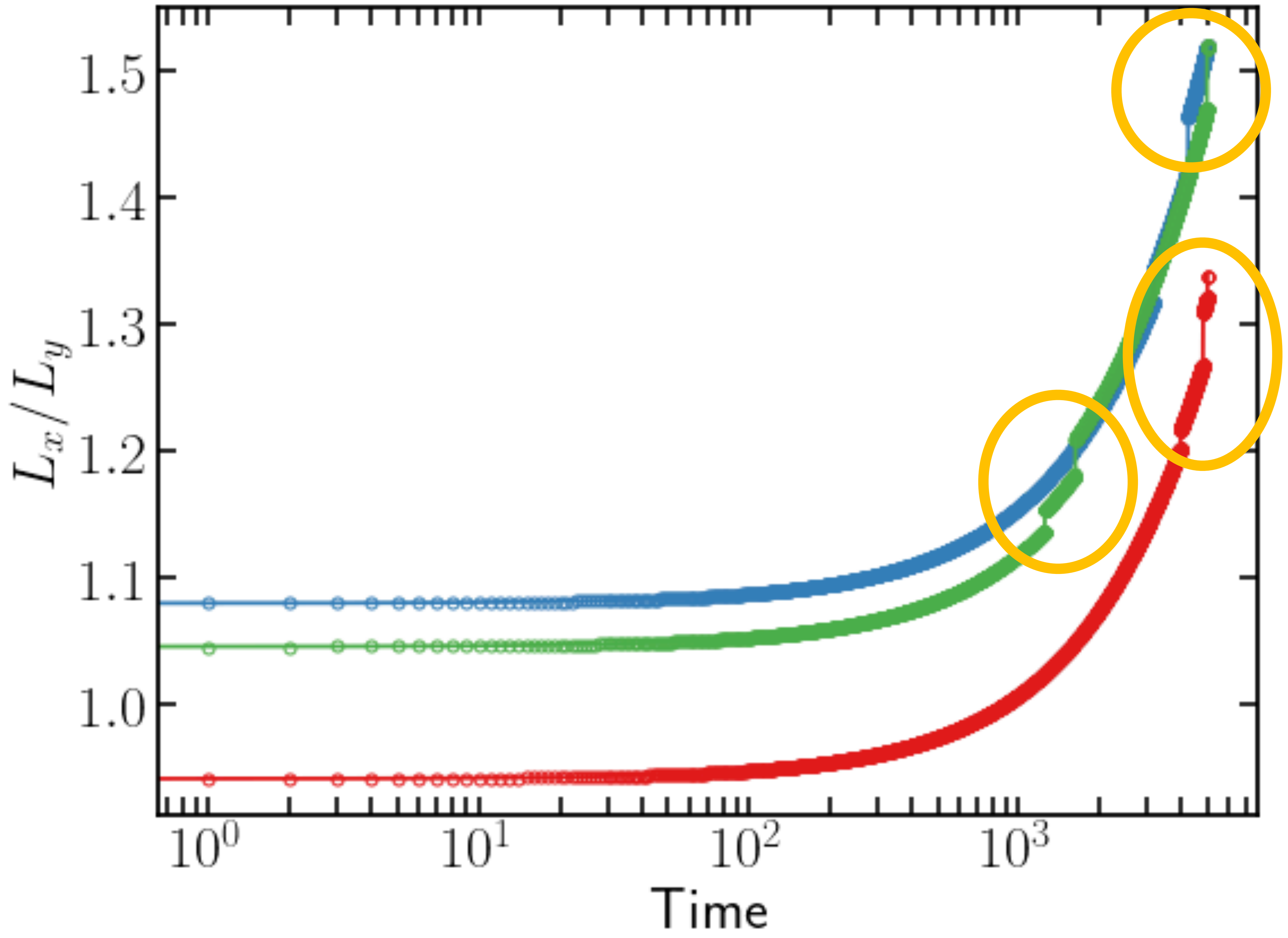
Aspect ratio



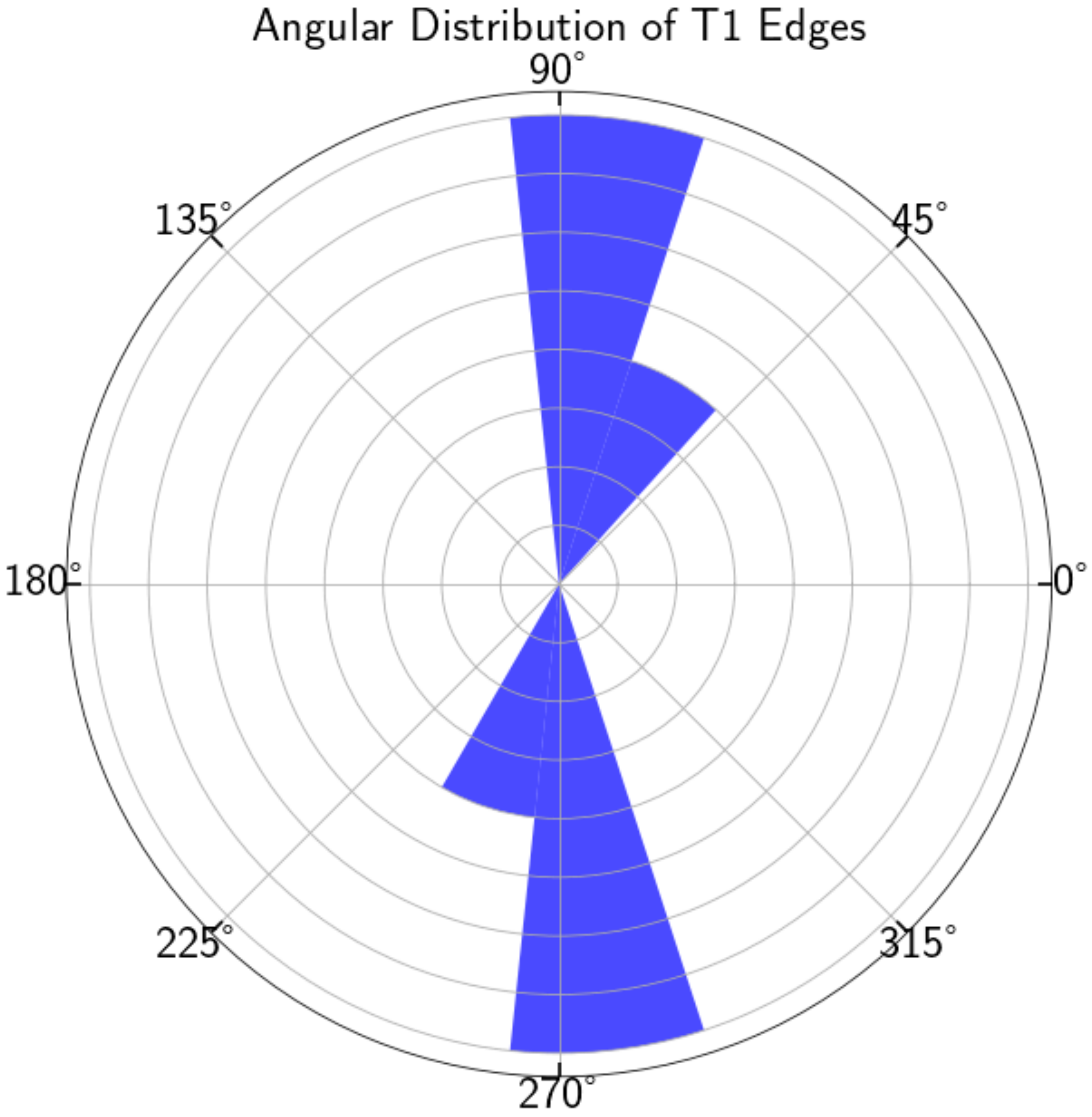
Convergent Extension Accompanied by T1 events

The snapping points correspond to T1 events

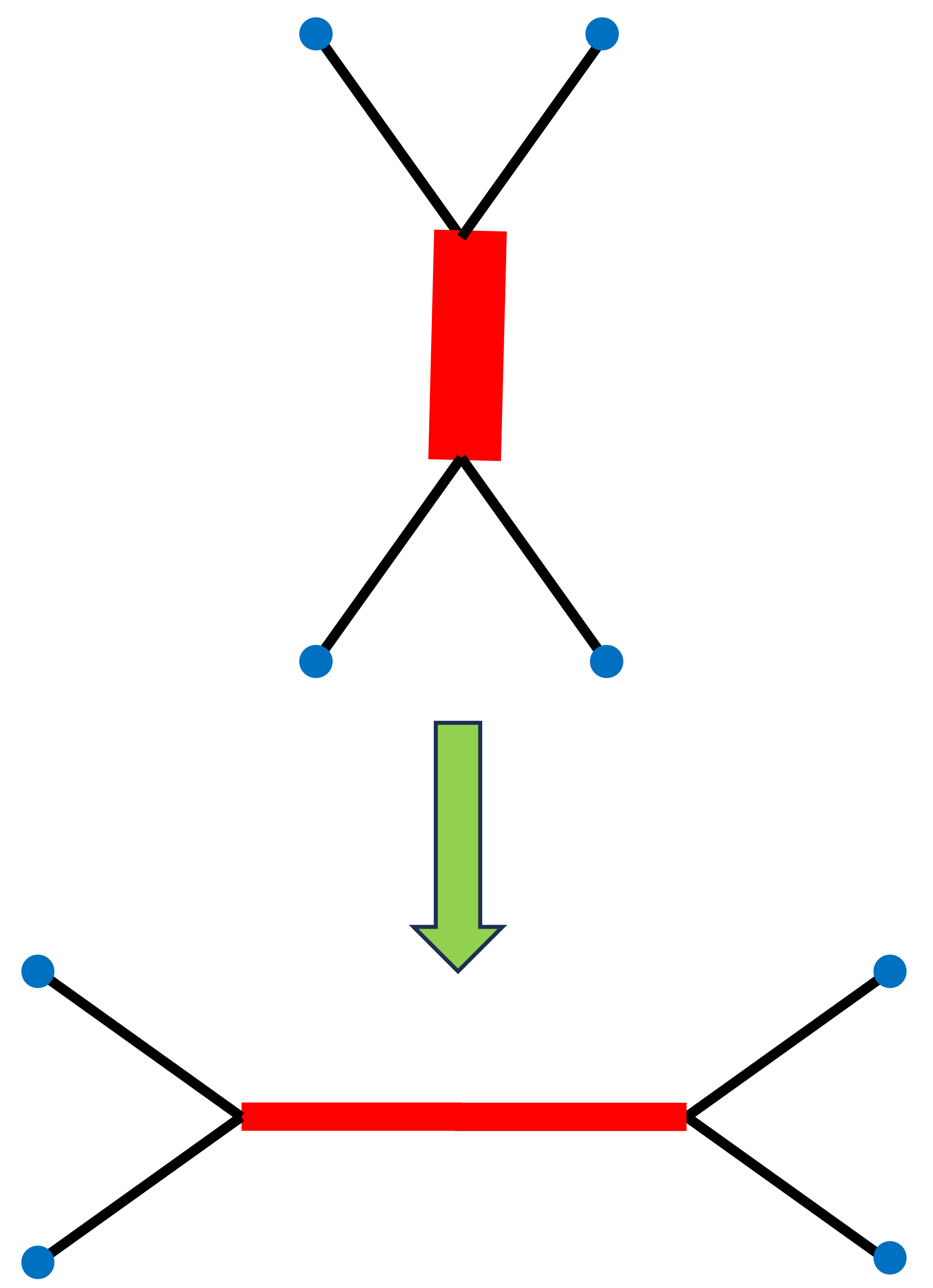


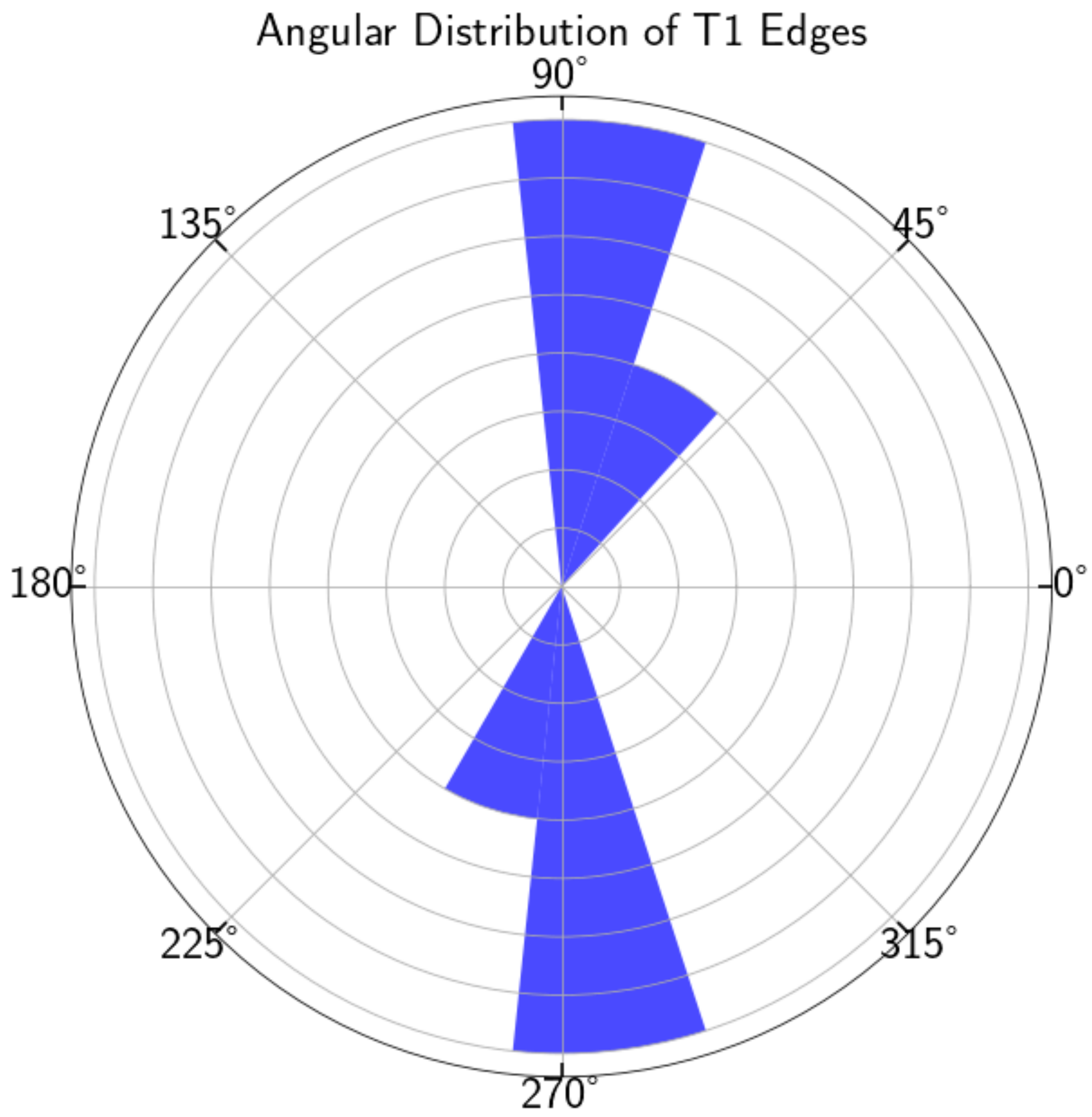


T1 Events Are Oriented



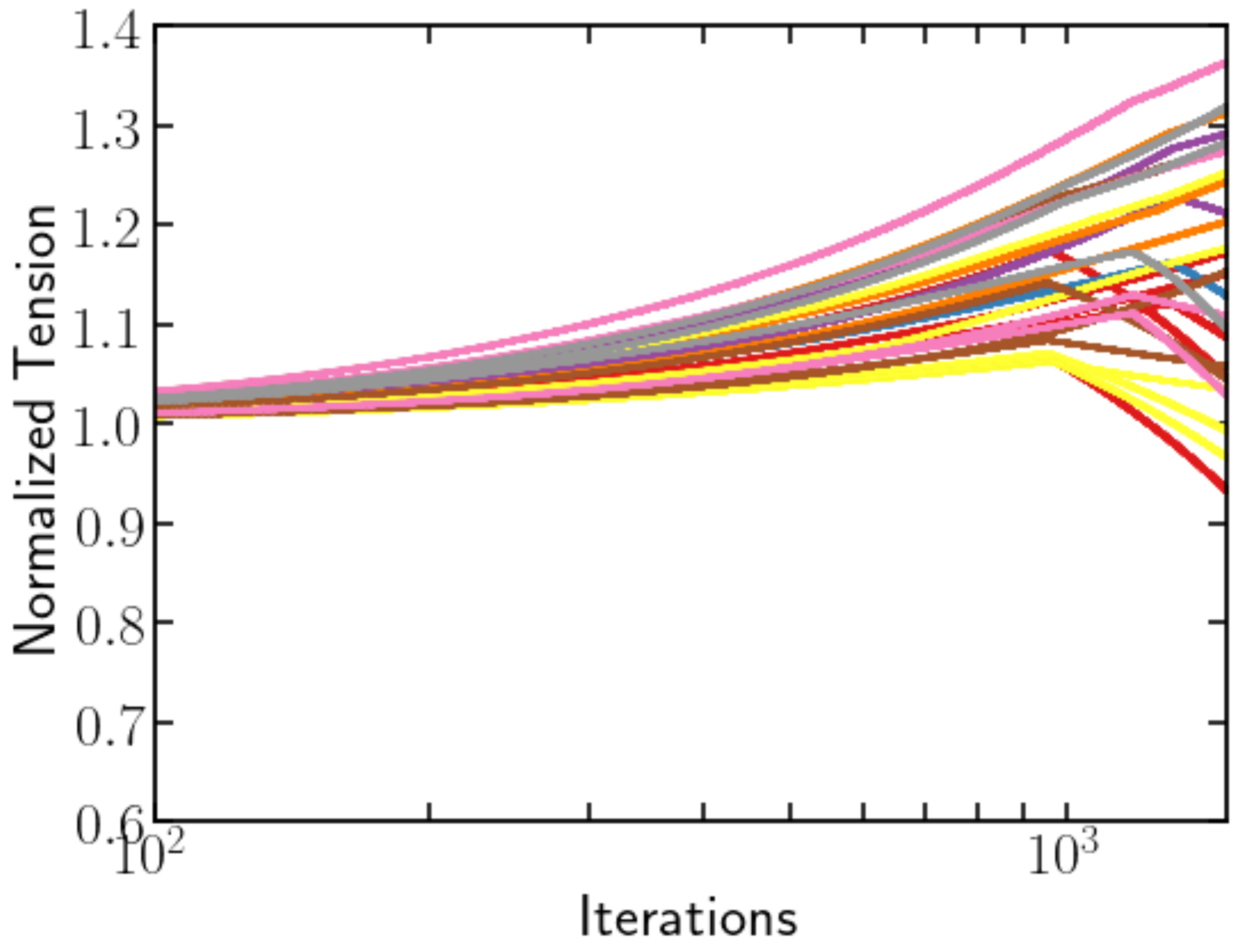
T1 Events Are Oriented





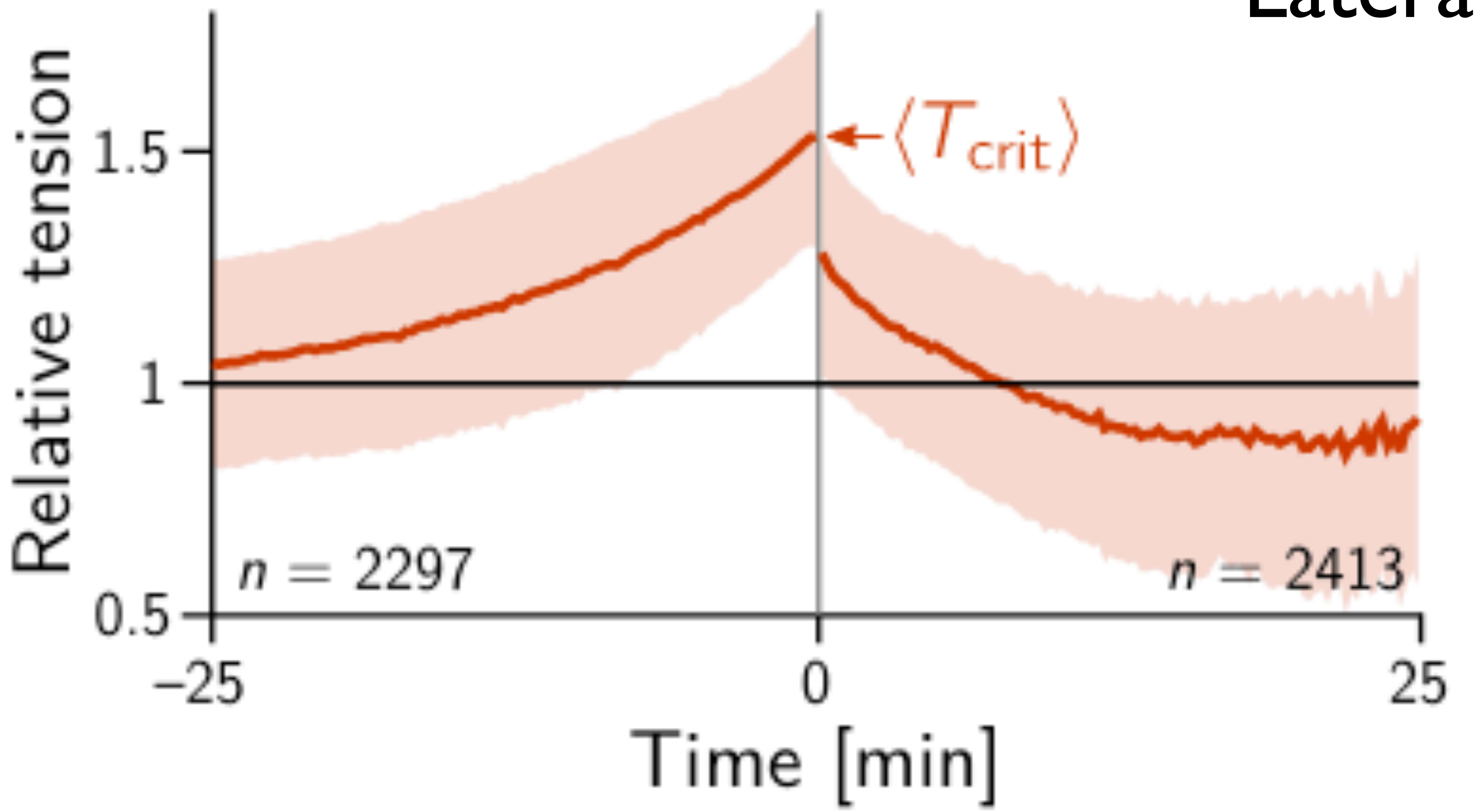
Tension on Vanishing Edge Increases Before T1 event

They all show an increasing trend of tension before undergoing T1



Similar to Active T1s

Lateral ectoderm: active T1s



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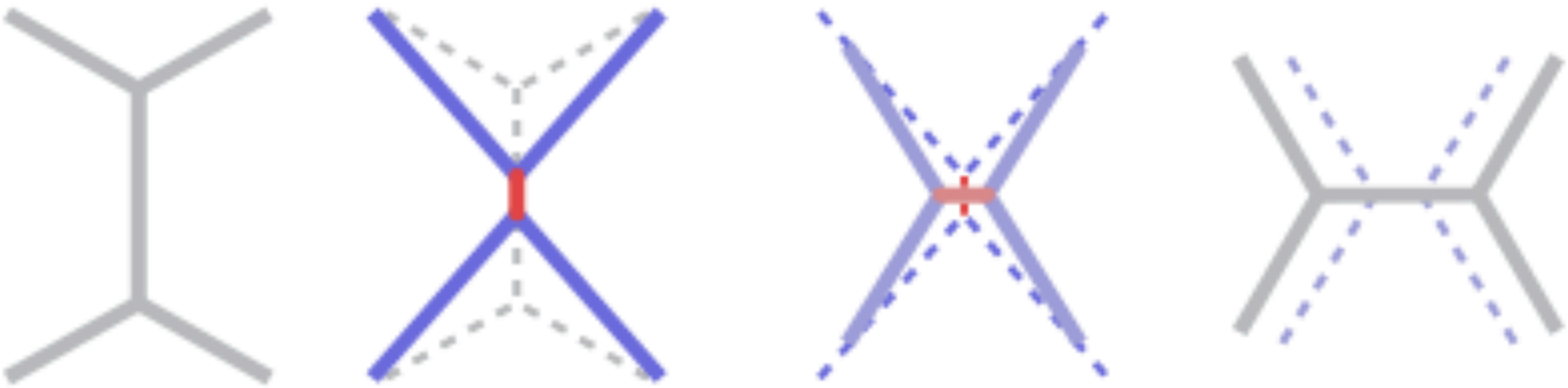
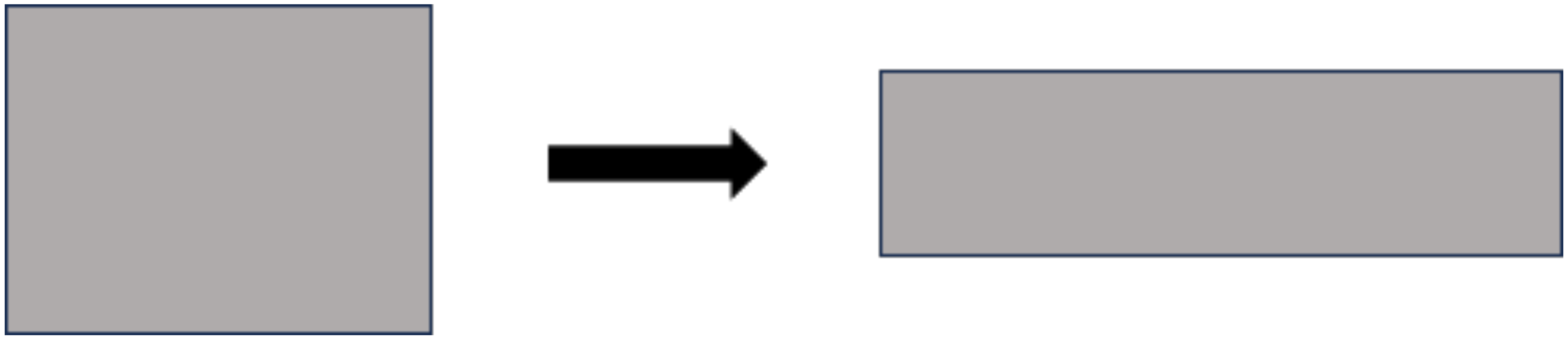


Brauns ++ bioRXiv (2023)

Compare to Applying Global Shear to Vertex Model



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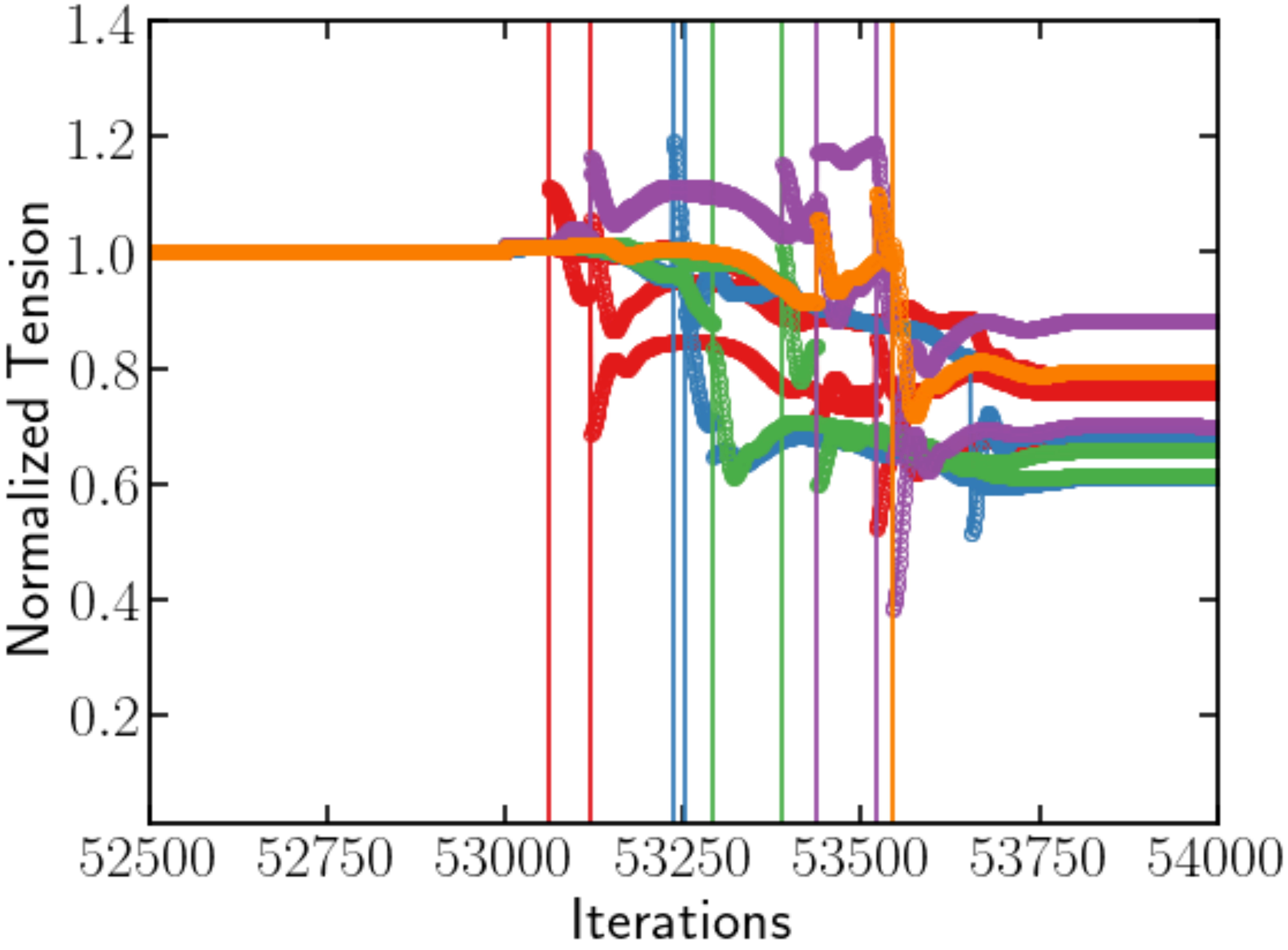
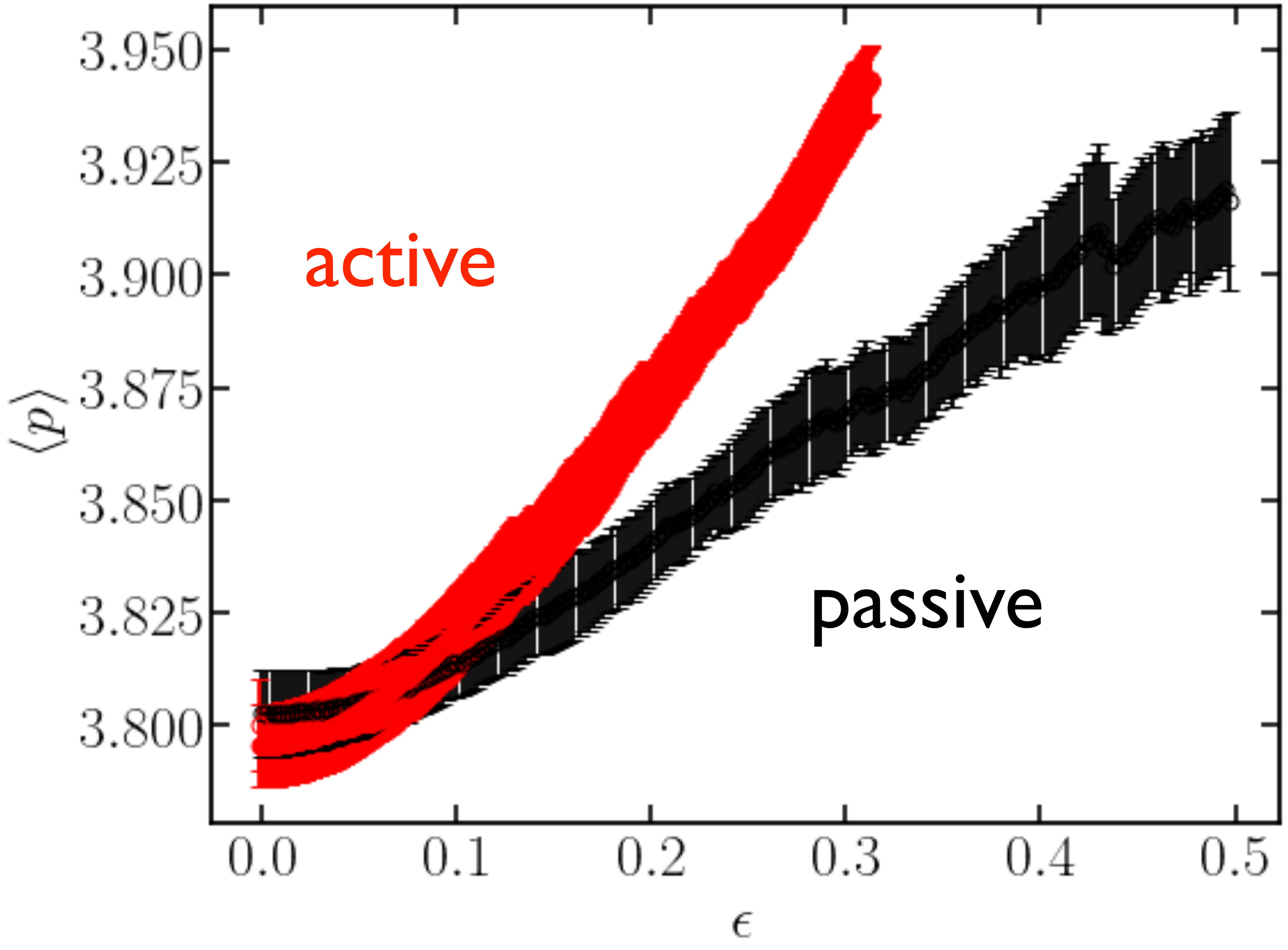
Tension on Vanishing Edges Remains Flat Before T1

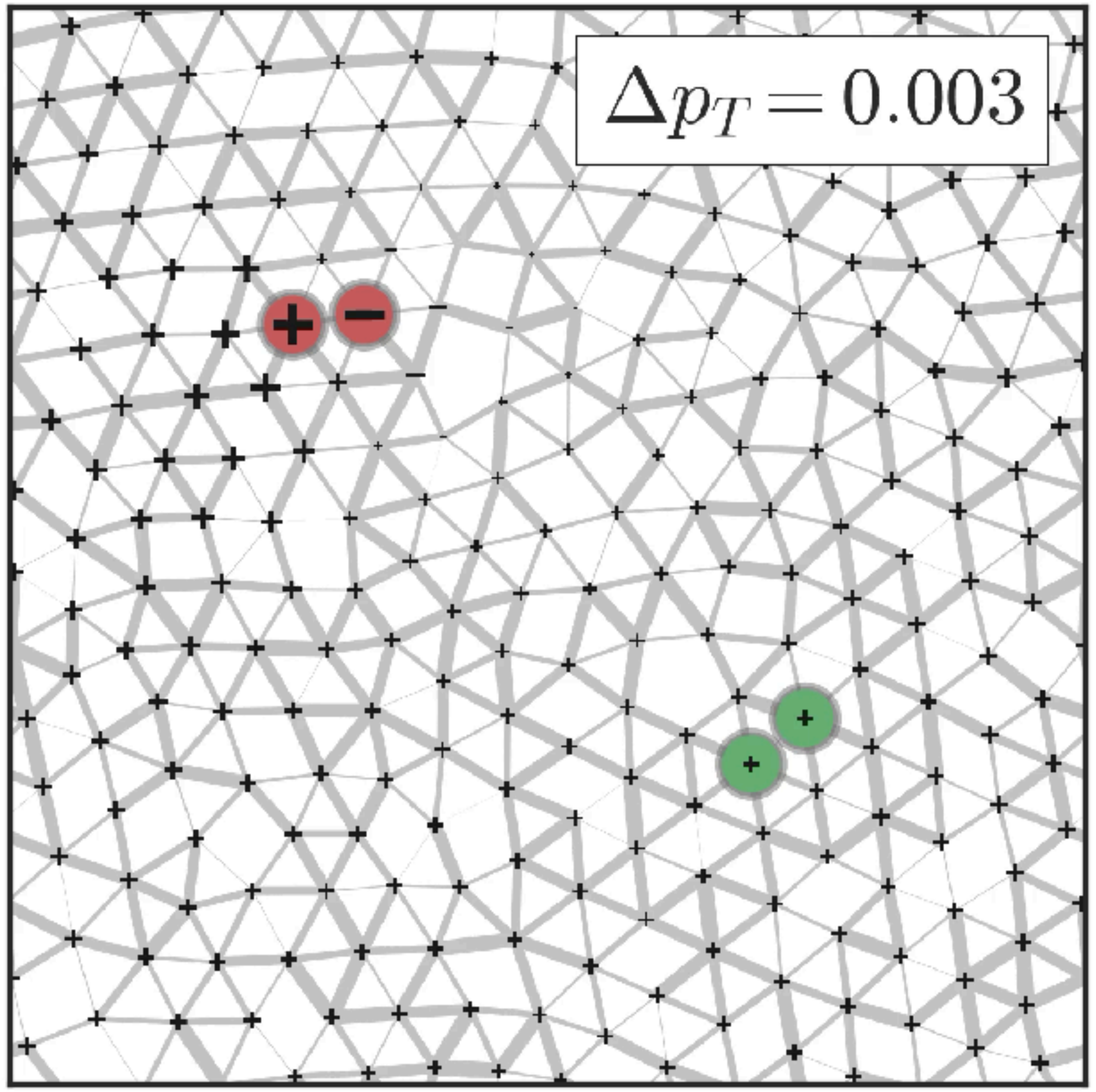


Different Mean Shape Factors During Active vs. Passive Extension



Double Optimization: Is Many More Different?

- Cost function: $\mathcal{C} = (\Delta - \Delta p_T)^2$
- Parameters: edge conductances
- Physical cost function: dissipated power
- Physical DOF: node pressures or edge currents
- 1st optimzn: Minimize power wrt physical DOF —required by physics!
- 2nd optimzn: Use gradient descent to minimize control cost function wrt control DOF



Is many more different?

Tune for N_T targets with response Δ

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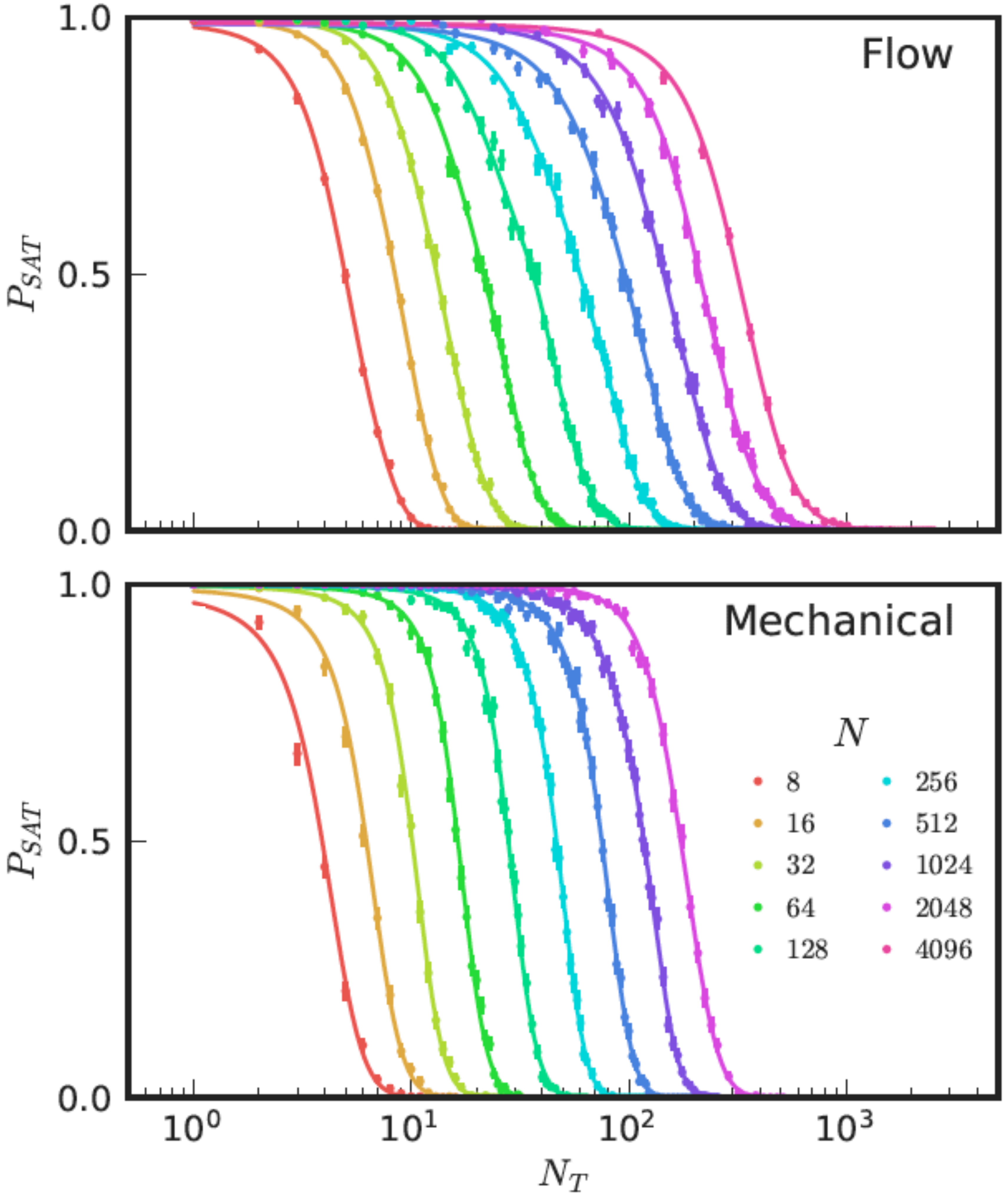
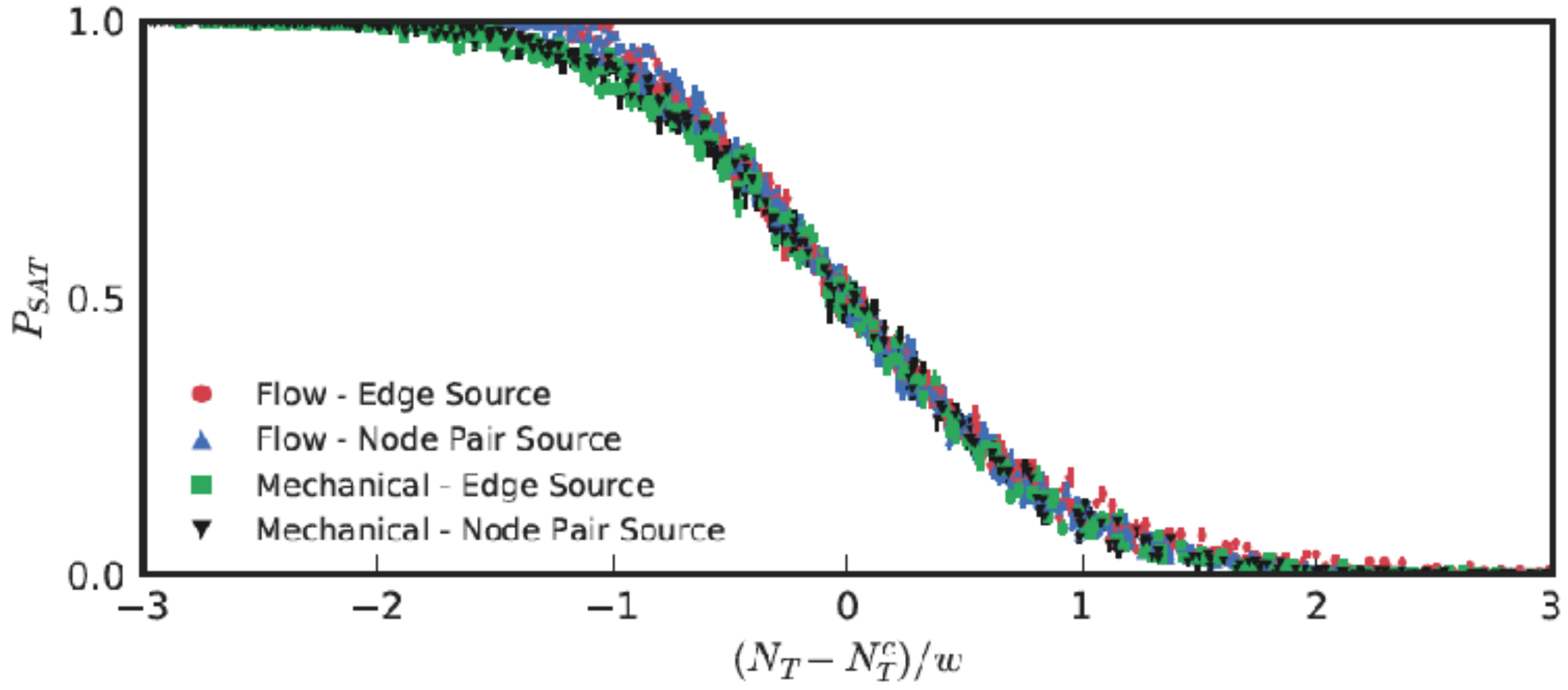
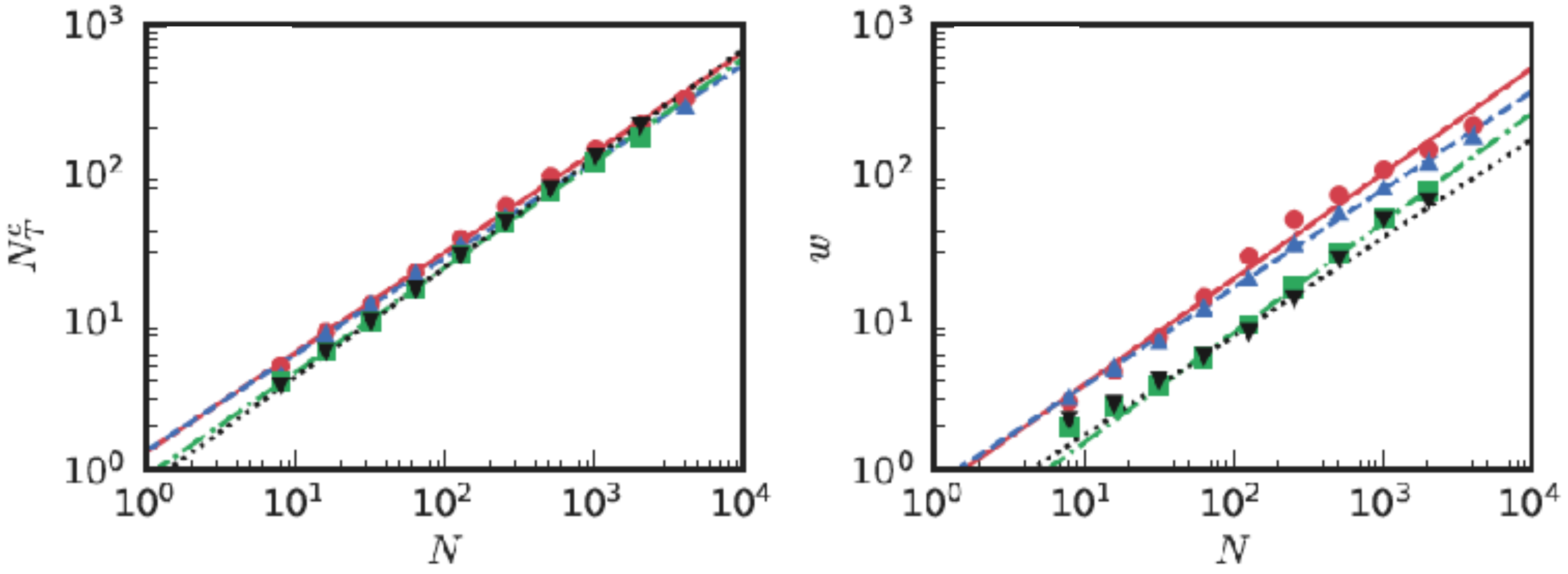
Rocks, Ronellenfitsch, Liu, Nagel, Katifori PNAS 2019

Yes: Many More is Different

- System can satisfy more targets as system size increases







$N_T^c \sim N^{0.65\text{-}0.71}$

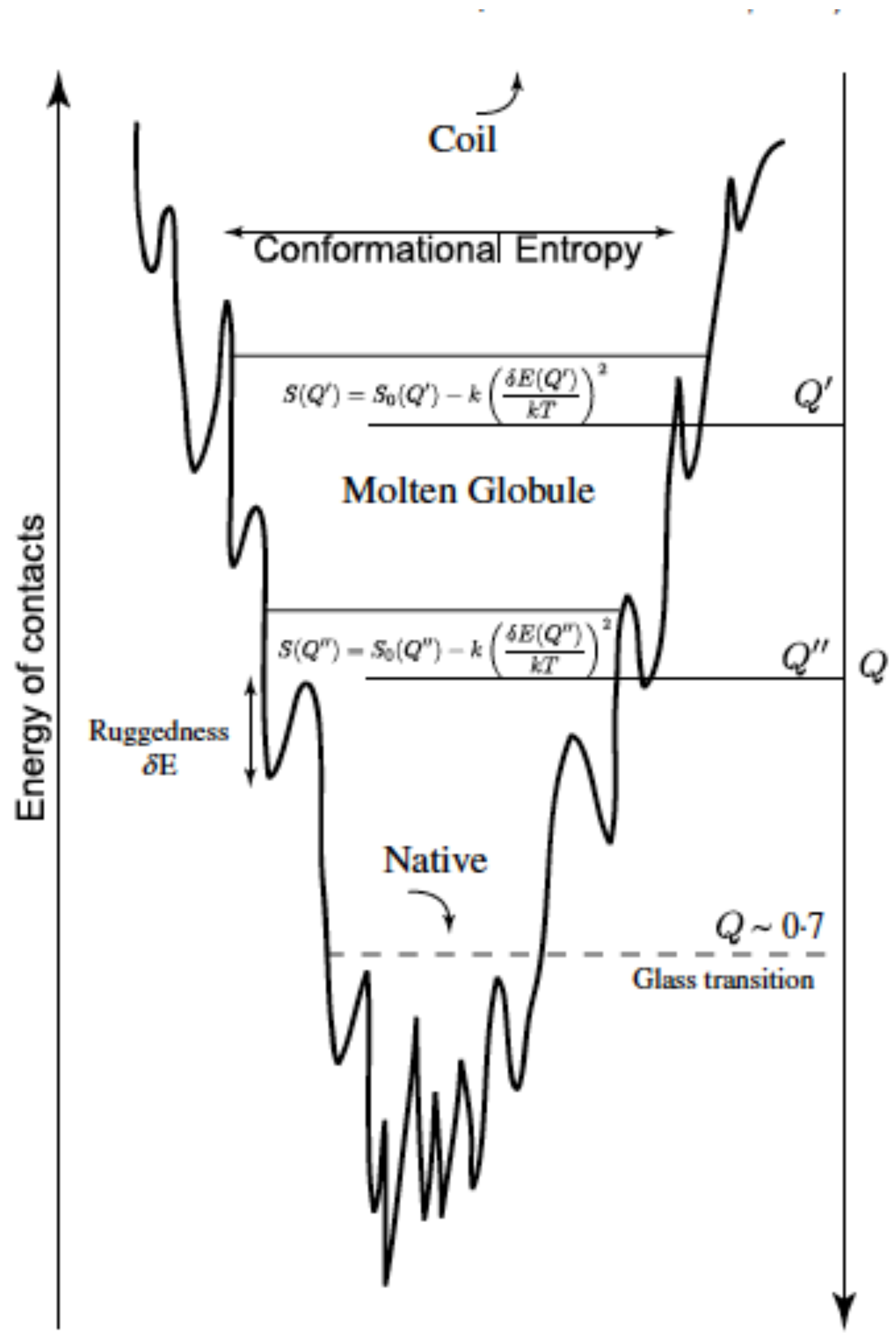
$w \sim N^{0.66\text{-}0.74}$

Rocks, Ronellenfitsch, Liu, Nagel, Katifori PNAS 2019

Many More is Indeed Different

- But many more is different in a familiar way—a phase transition (constraint-satisfaction transition)
- But here we have 2 sets of DOF—parameters + physical DOF
- Does that change anything?

Yes it can: Funnel Landscape Inspired by Protein Folding



Onuchic, et al 1995

- Instead of minimizing

$$\mathcal{F} = \sum_{i=1}^{N_T} (\Delta - \Delta V_i)^2 \Theta(\Delta - \Delta V_i)$$

- minimize

$$\hat{\mathcal{F}} = \sum_{i=1}^{N_T} \frac{1}{R_i^{2\beta}} (\Delta - \Delta V_i)^2 \Theta(\Delta - \Delta V_i)$$

R_i is distance from target *i* to source

- This provides funnel in space to tune targets in order of distance from source

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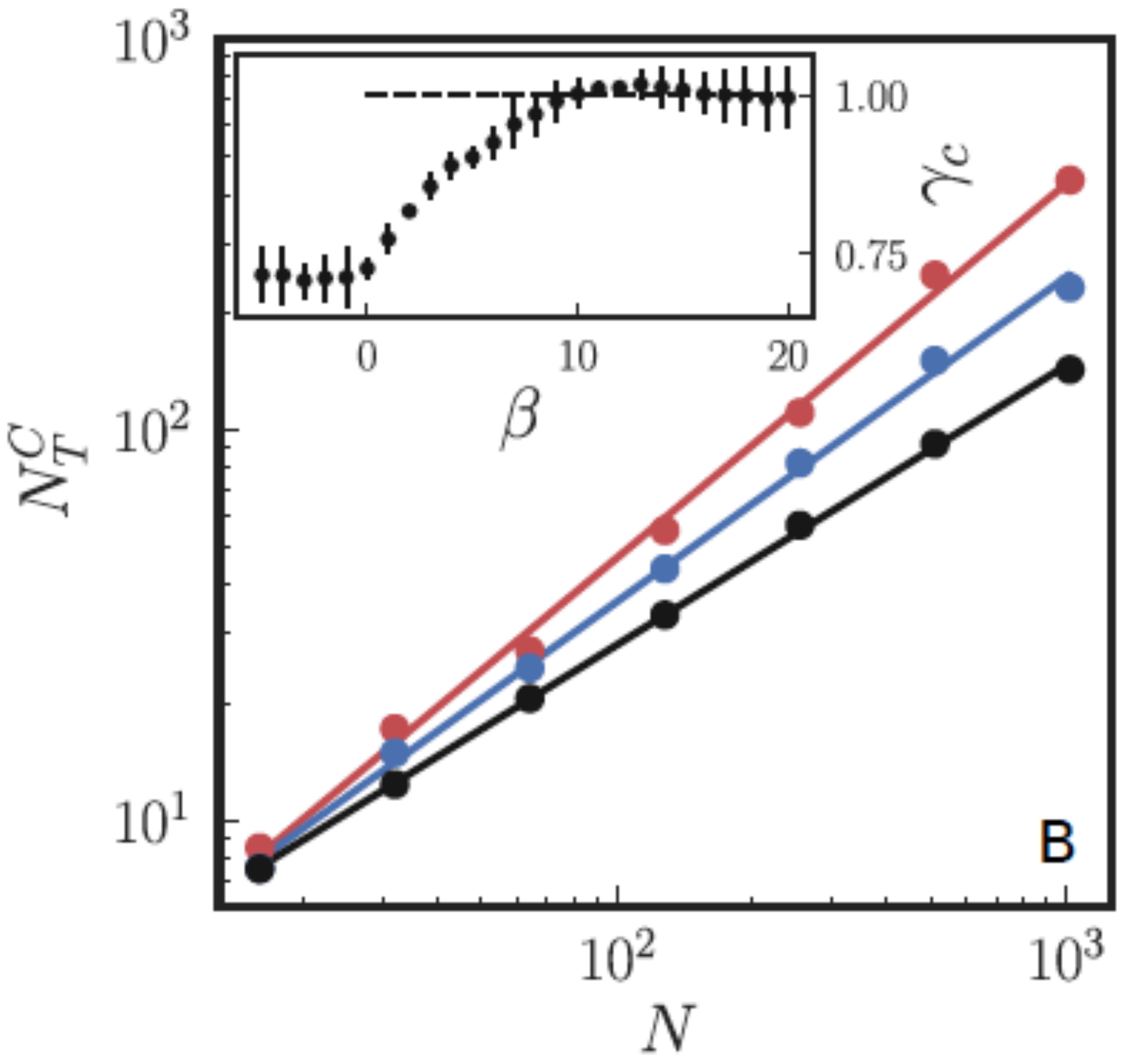
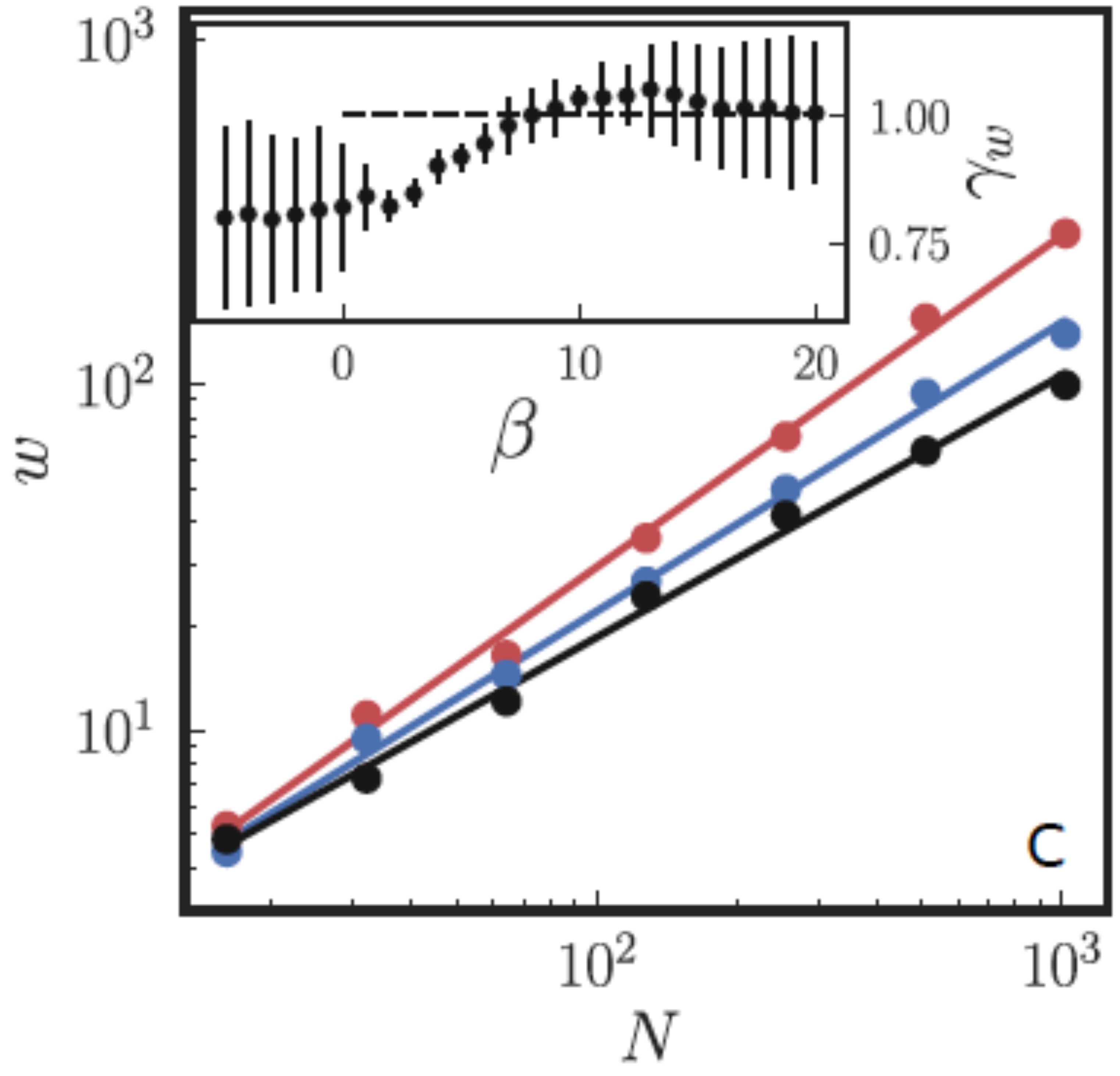
M Ruiz Garcia, AJ Liu, E Katifori PRE (2019)

Changing Cost Function Changes N-Dependence!

- Steepness of funnel controls scaling

M Ruiz Garcia, AJ Liu, E Katifori PRE (2019)





- For large β, $N_T^c \sim N$ and width/N is constant as $N \rightarrow \infty$ (same as Hopfield)
- SAT/UNSAT transition is not sharp

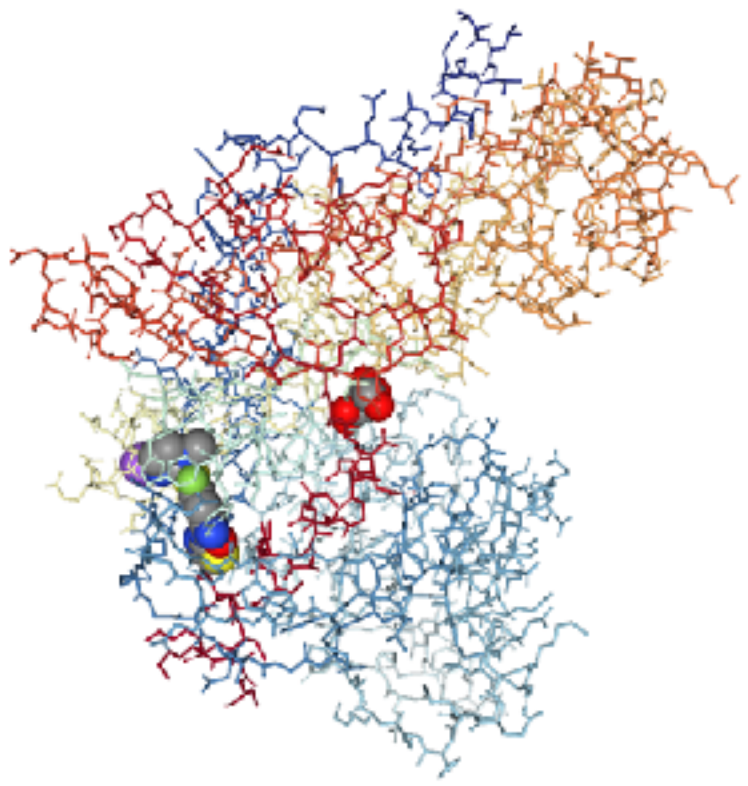
How many more is different is subtle and needs to be understood

Summary

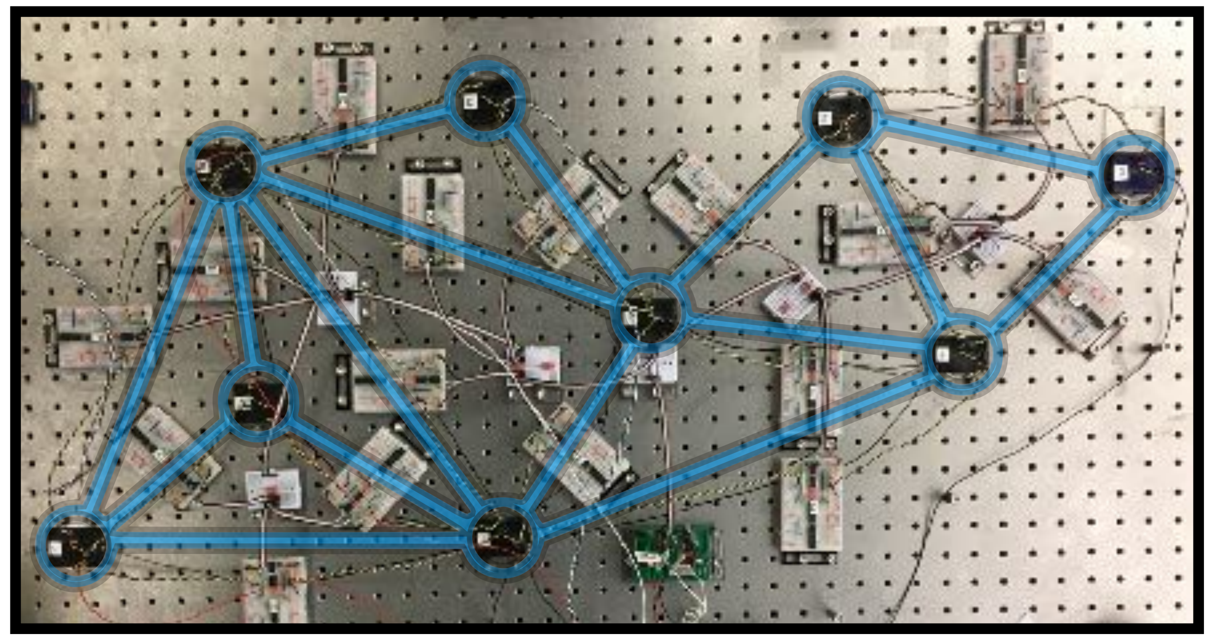
- Simultaneous optimization of cost function and physical Lypunov function provides systematic way of solving inverse design problems: very general
- Biological systems with adaptive function use local rules to adjust parameters
  - What are the parameters?
  - What is the process by which they are adjusted??
- Unusual kind of condensed matter
  - Many more is different because more constraints can be satisfied with more parameters
  - But nature of constraint-satisfaction transition depends on cost function and we don't know what it is in biological contexts
- Important for understanding function in living matter
  - Speculation: biology stays in overparameterized regime
    - Easiest to introduce extensive number of parameters
    - Easy to get good solutions in overparameterized regime
    - Good solutions are more generalizable with many flat directions & representational drift

Learning about Learning Metamaterials

Andrea J. Liu
University of Pennsylvania



Felipe Rodrigues Martins	UPenn
Marcelo Guzman	UPenn
Nachi Stern	UPenn
Jason Rocks	UPenn/BU
Vijay Balasubramanian	UPenn
Eleni Katifori	UPenn



GO TO SLIDES

Thanks to

Jason Rocks

Menachem Stern

Marcelo Guzman

Felipe Martins

Eleni Katifori

Vijay Balasubramanian

DOE Biomolecular Materials

NSF DMR Materials Theory

NSF UPenn NRT

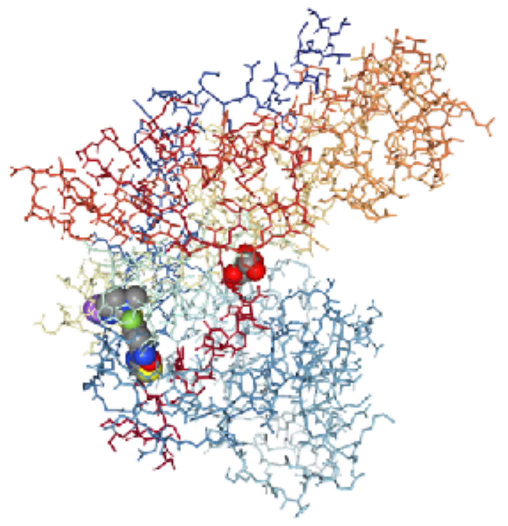
Simons Foundation

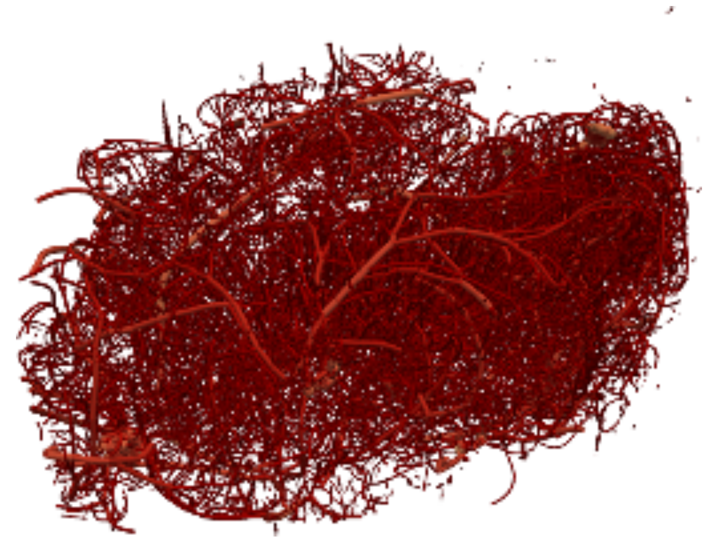
How do input/output responses emerge as collective phenomena?

- Goal of stat phys: to gain microscopic understanding of macroscopic (collective) phenomena in many-body systems
- This requires
  - Reducing microstate information (e.g. positions and velocities) to averages/variances (distributions) of relevant microscopic quantities (eg order parameters)
- For over a century, statistical physics has provided
  - solution to dimensional reduction problem
  - bridge between micro & macro scales via relevant micro variables
- But some problems resist statistical physics
  - Far from equilibrium
  - Complex landscape
  - Correlated disorder

Input/Output Problems are Resistant to Statistical Physics

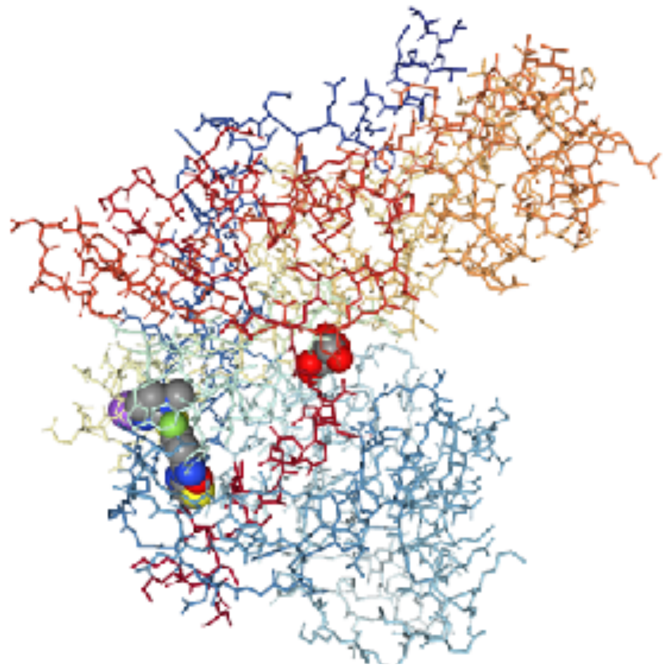
- For protein allostery
  - there are 20 different amino acids at each site (adaptive DOF)
  - amino acid sequence (values of adaptive DOF) not chosen randomly but by evolution/natural selection
- For flow allostery
  - there are 10^6 edges in brain vasculature with range of potential conductances for each
    - vasculature does not choose conductances (adaptive DOF) randomly but to satisfy input/output relations
- We need new approaches for these hard problems

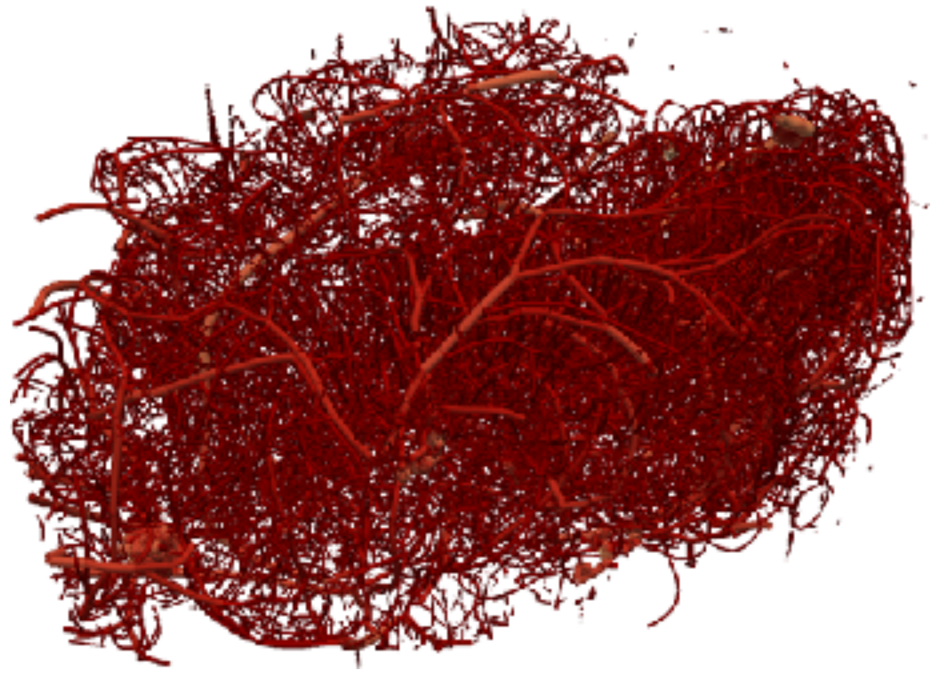




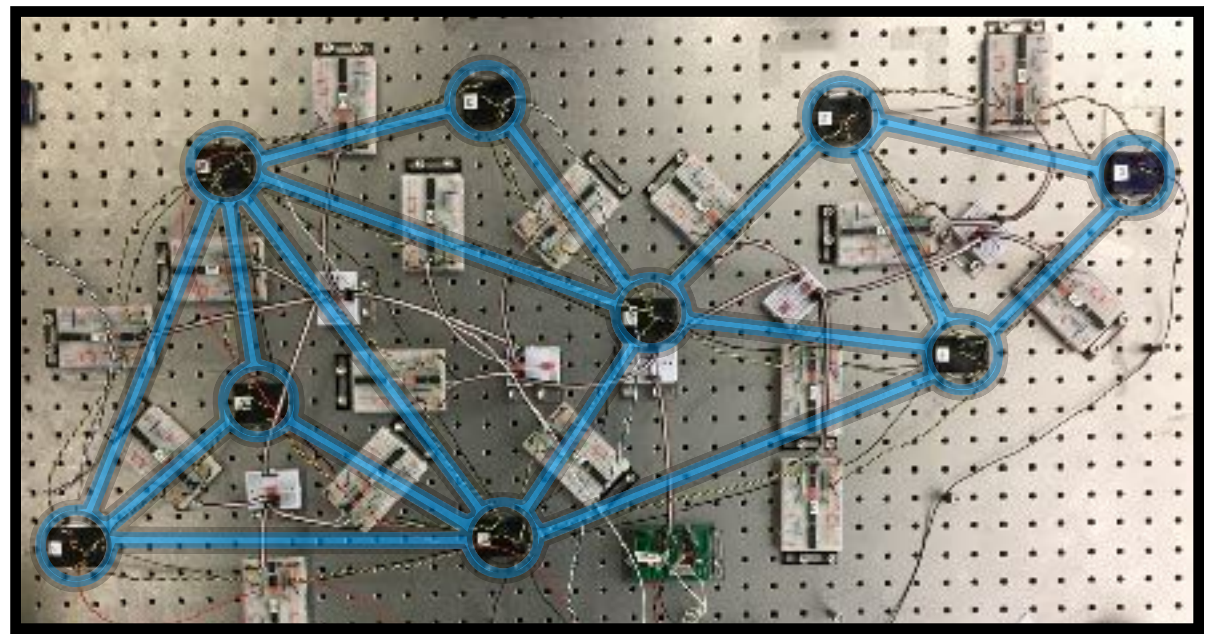
Input/Output Problems Require Ensembles

- "Stat Phys" requires ensembles
  - Here we need big designed/evolved ensembles
- We have protein families across species
- But these are small by stat mech standards
- New material design approach allows us to construct large ensembles! "statistical physics"
  - Consequence of overparameterization





Goodrich PRL 2015
Rocks PNAS 2017
Hexner Soft Matter 2018
Hexner PRE 2018
Rocks PNAS 2019
Pashine Sci Advances 2019
Pashine Hexner PRR 2020
Hexner PNAS 2020
Rocks PRL 2021
Rocks PRR 2020



What Do We Want "Statistical Physics" To Answer?

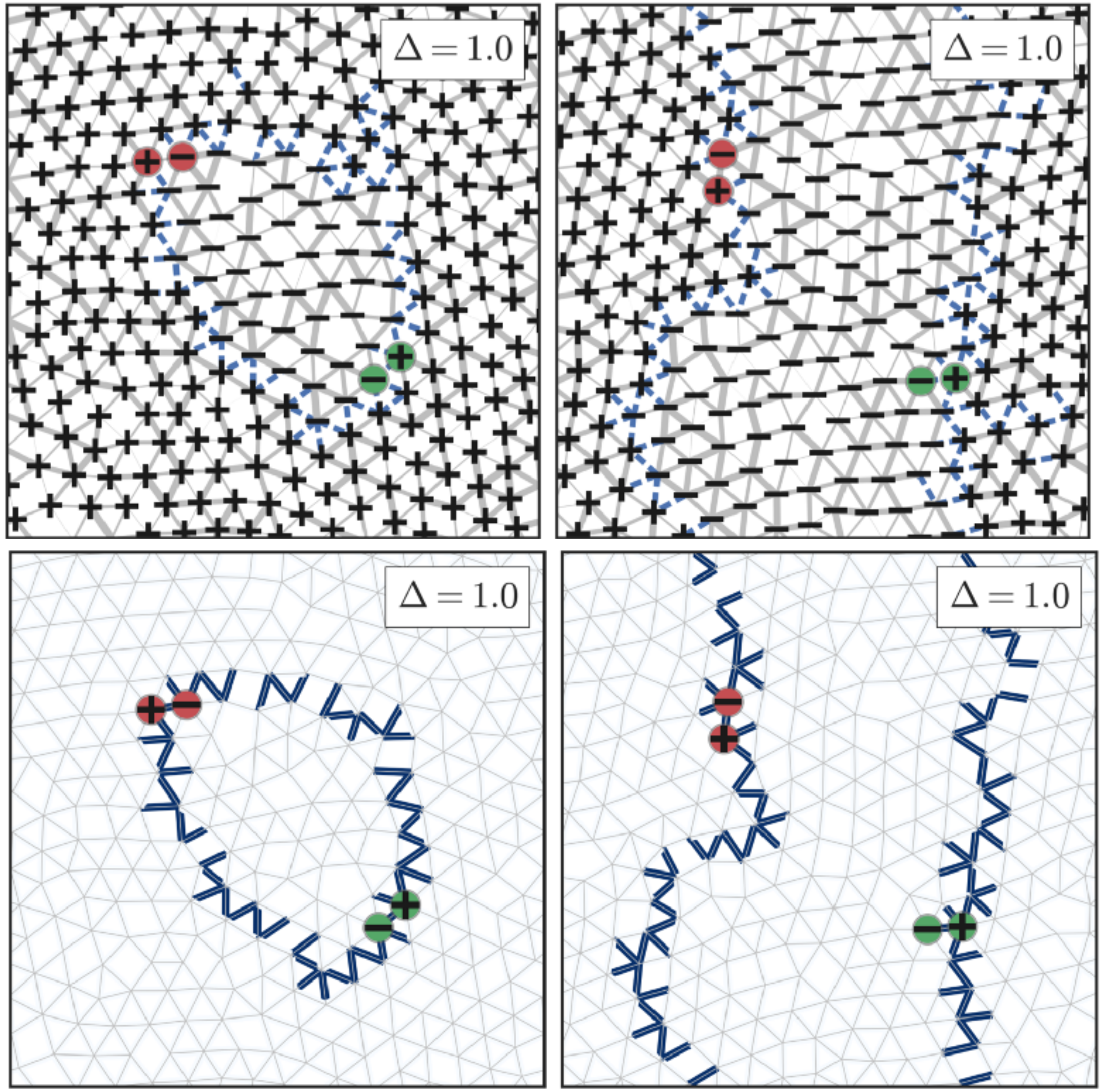
- We now have designed ensembles
- So what do we want to know??
- How does edge tuning at microscopic scale lead to emergent collective phenomenon of function at macroscopic scale?
- What happens to networks when they learn function?

- Where to start?

GO TO SLIDES

Where to Start in Learning about Learning?

- When in doubt, look at simplest case in extreme limits
- Consider 1 source edge with ΔV=1 and one target edge with ΔV=Δ=1
- System partitions into two regions of constant voltage separated by low-conductance barrier



Rocks, Liu, Katifori PRL 2021
Rocks, Liu, Katifori PRR 2020

Function Requires Simultaneous Minimization in Two Landscapes

- Both landscapes evolve during learning
  - Cost function depends on physical DOF (assumed equilibrated)
  - Power depends on adaptive DOF
  - Cost Hessian tells us curvatures in phase space of adaptive DOF

$$H_L = \frac{\partial^2 \mathcal{L}}{\partial k_i \partial k_j}$$

- Eigenvalues of H_L are curvatures, eigenvectors are corresponding directions in phase space of adaptive DOF
- This is much studied in stat phys of ML

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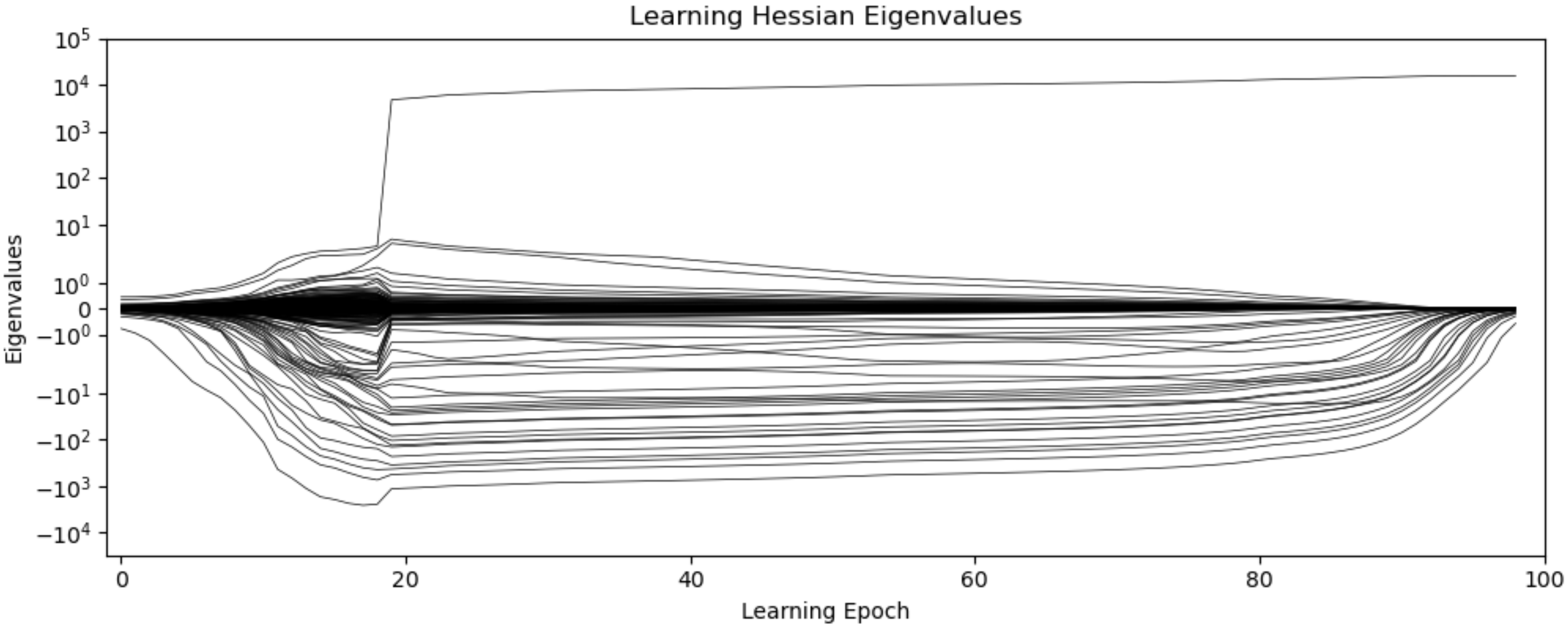
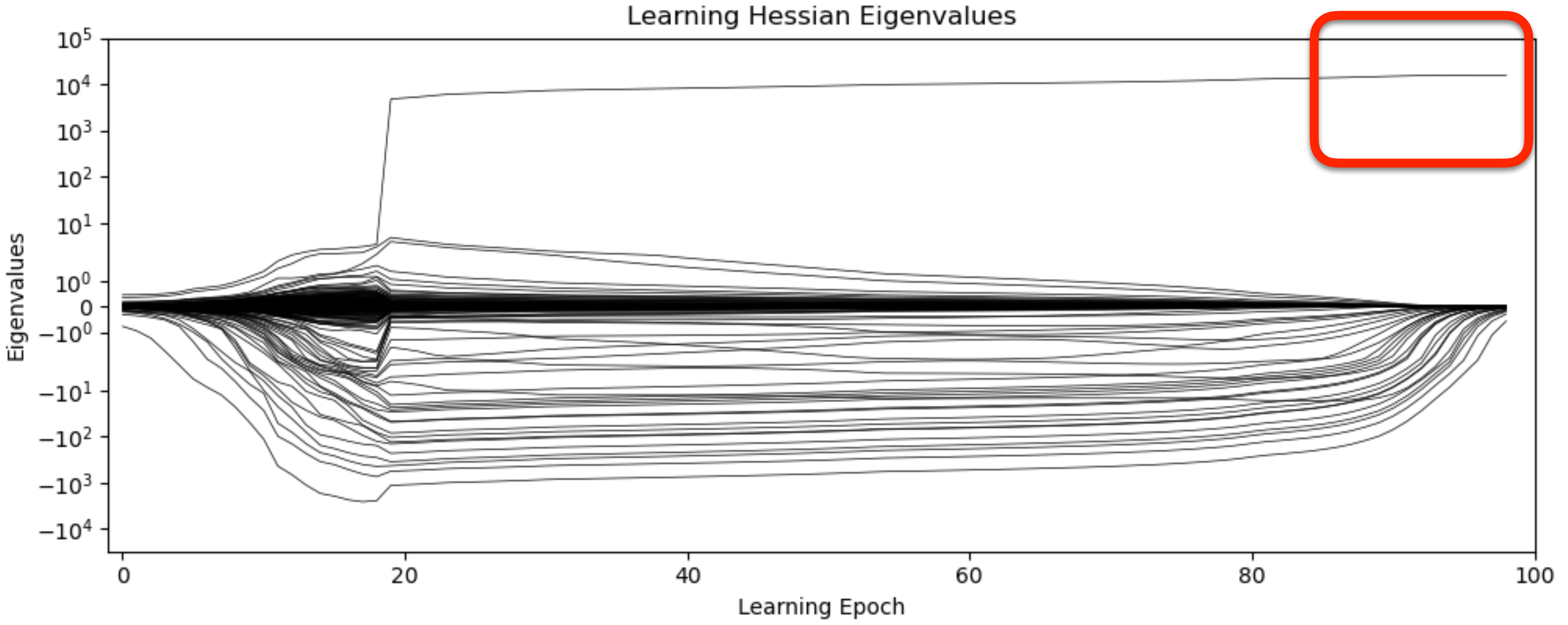
Cost Hessian Evolves During Learning



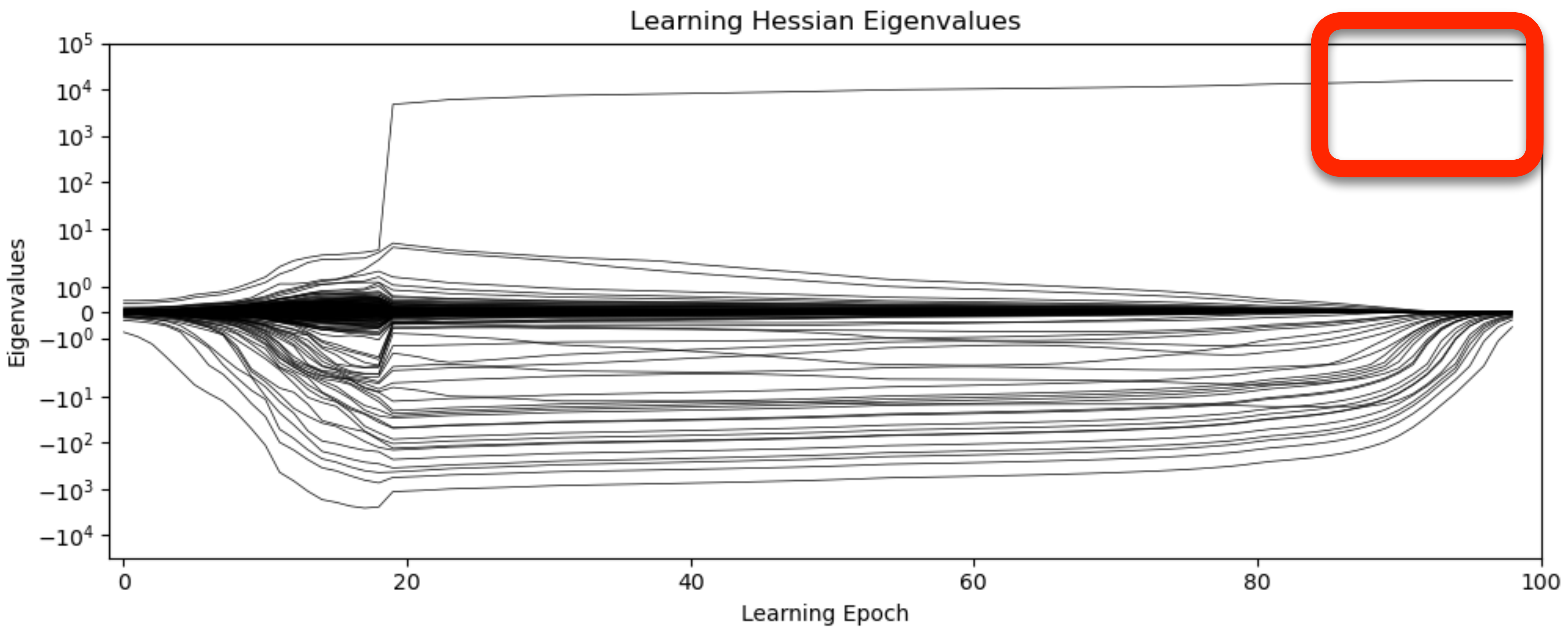
- Cost Hessian develops a gap at high end due to learning
- Highest eigenvalue reflects what was learned

Cost Hessian Evolves During Learning



- Cost Hessian develops a gap at high end due to learning
- Highest eigenvalue reflects what was learned

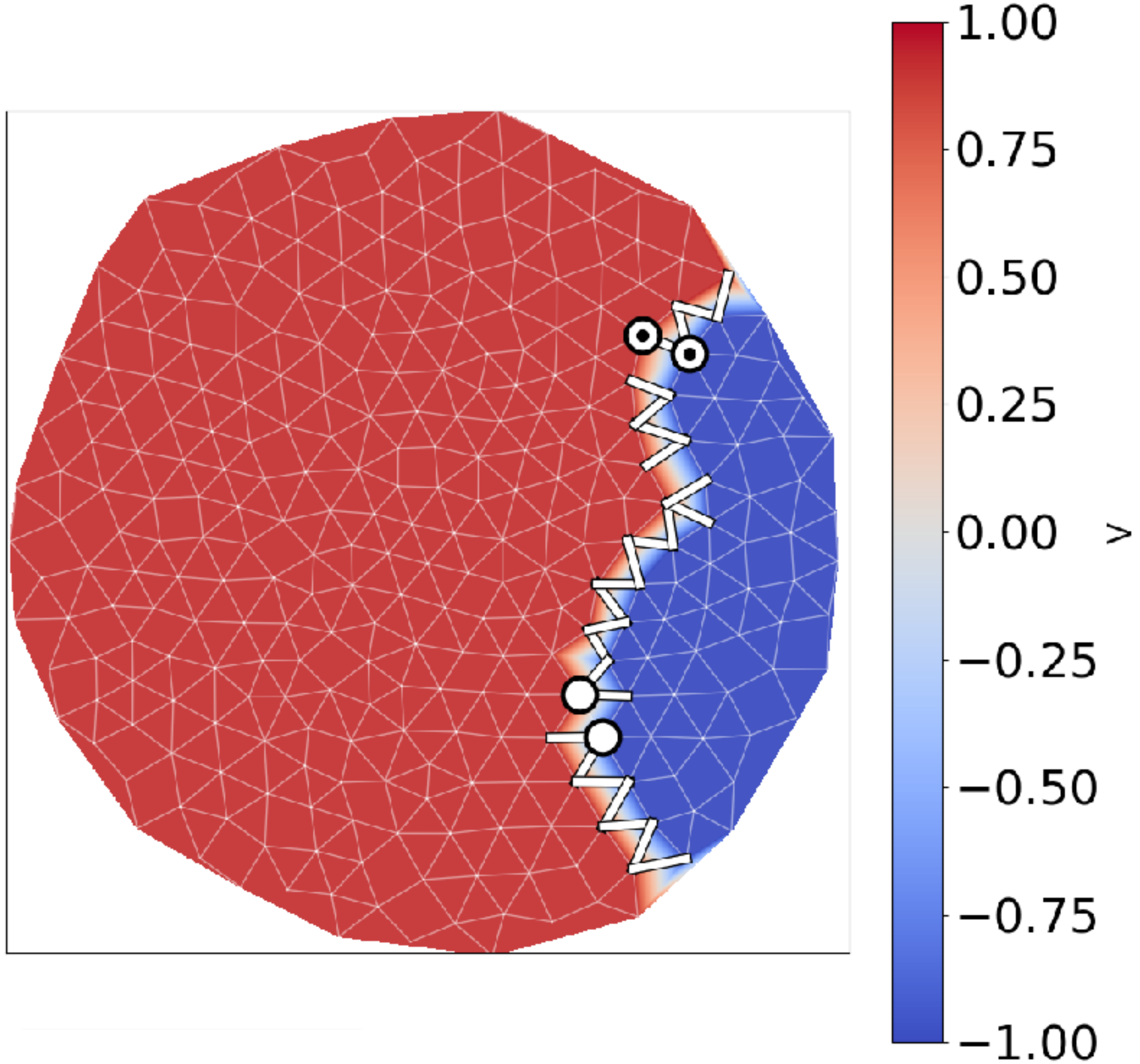
Highest Eigenvectors of Cost Hessian Capture Response



- In this extreme case, system divides into 2 sectors separated by low-conductance barrier
- Useful to verify we have captured the right physics
- But not what we want because it requires knowing learning cost function

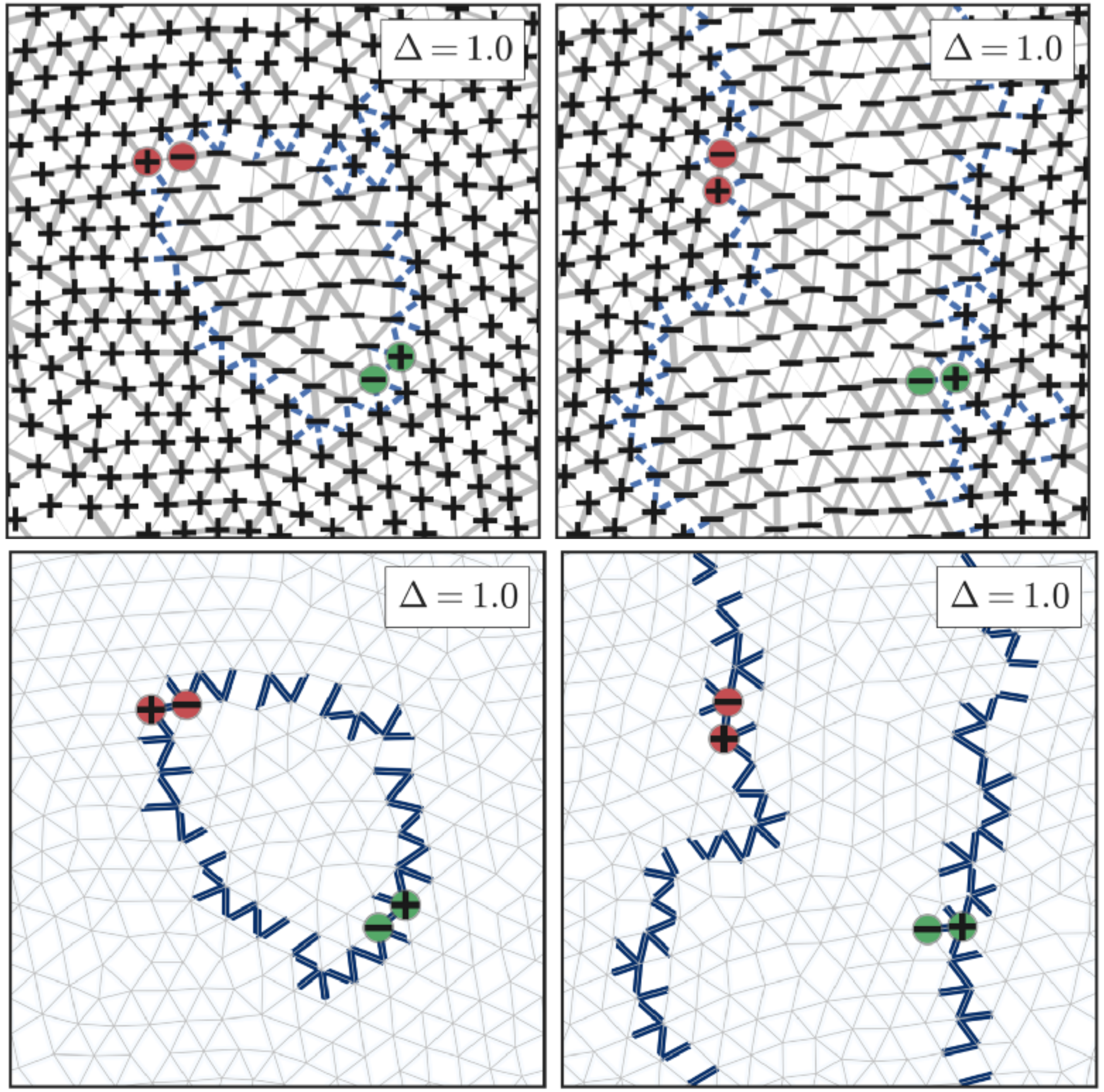
1 source edge: ΔV=1V

1 target edge: ΔV=1V



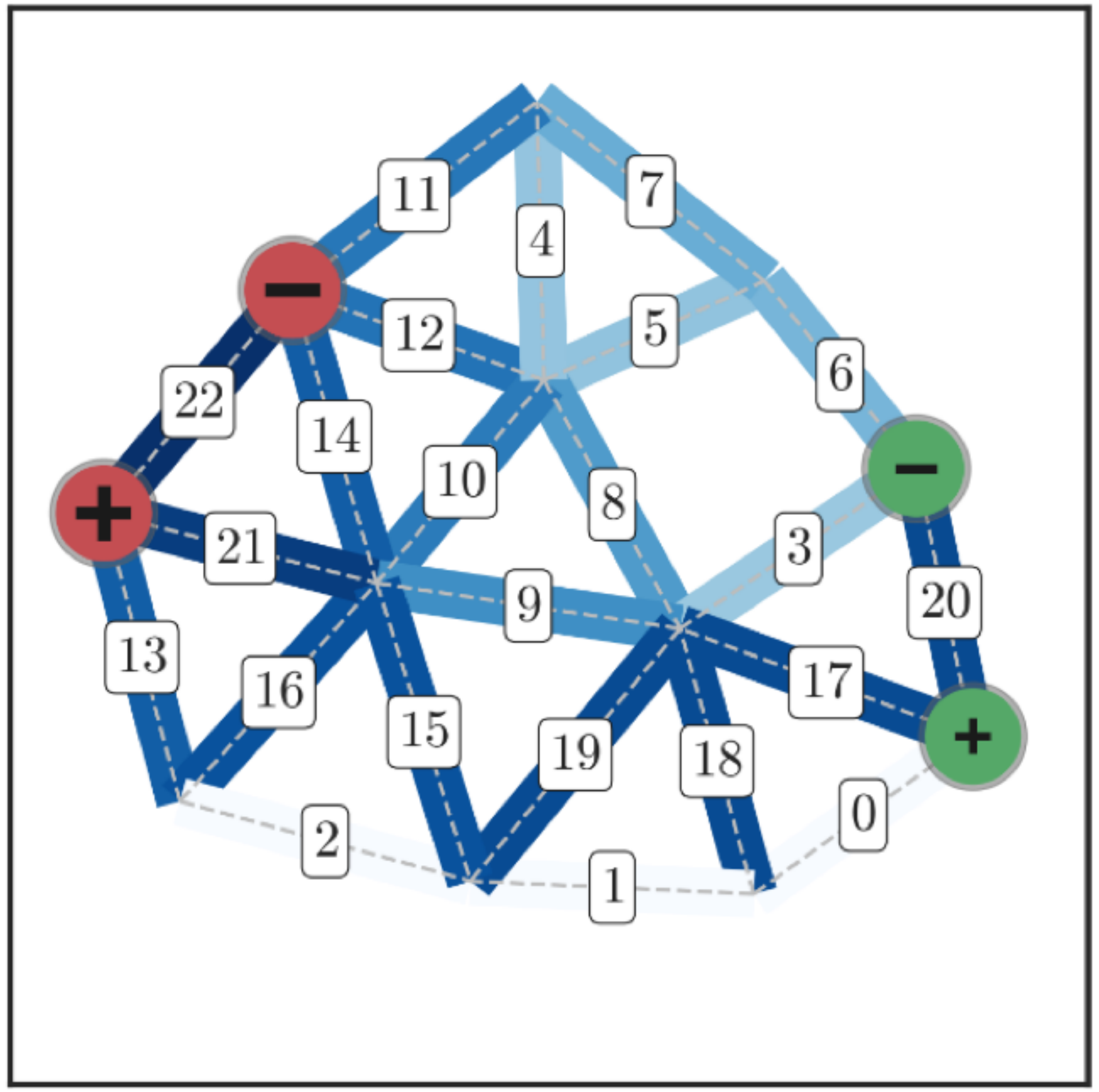
How to Capture Response Without Learning Cost Function?

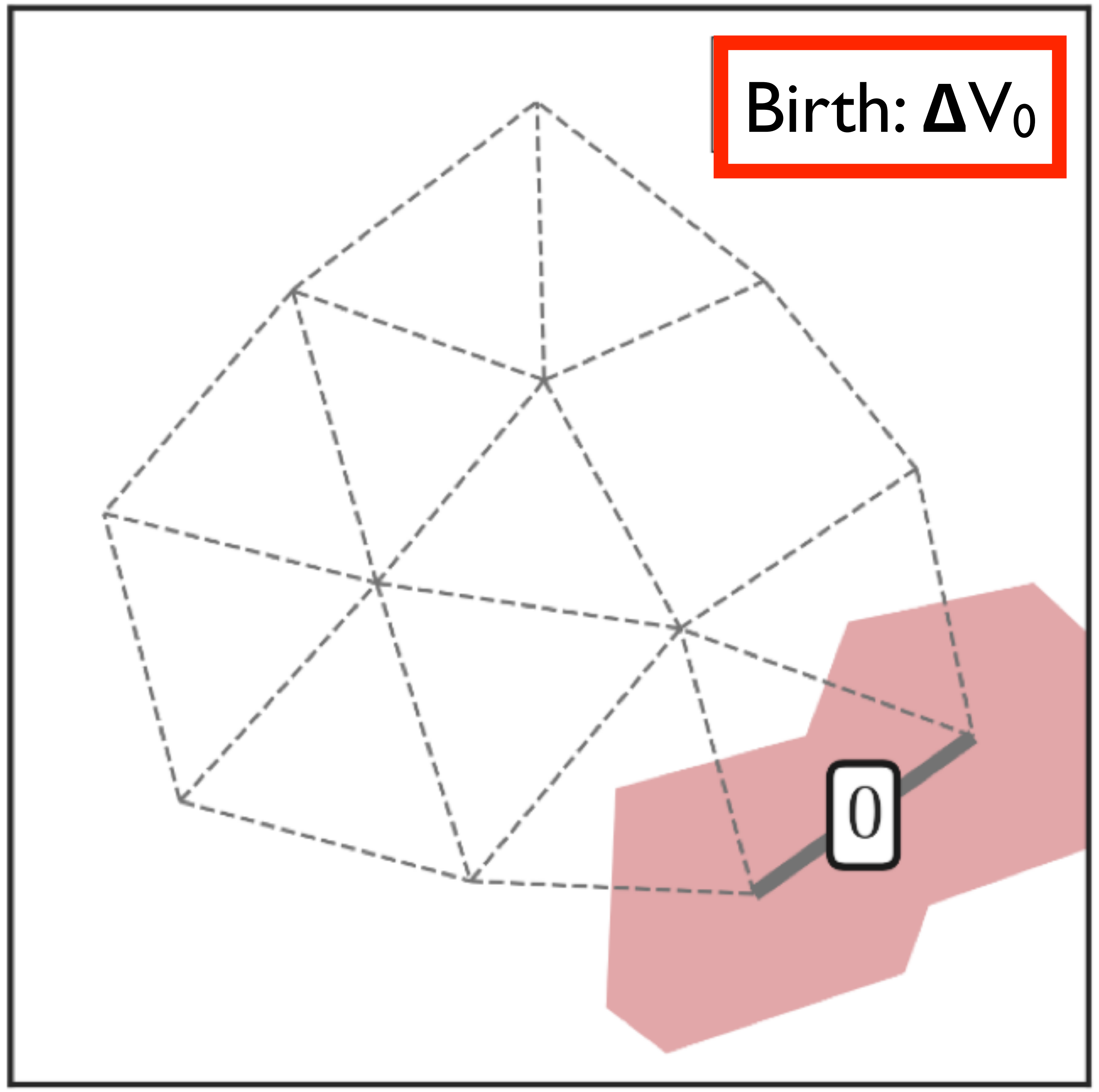
- For Δ=1, system partitions into two regions of constant voltage
- But what if Δ<1?
- In extreme limit Δ=1, edge-tuning/function relation is topological
- Use persistent homology to identify features responsible for function



Rocks, Liu, Katifori PRL 2021
Rocks, Liu, Katifori PRR 2020

Step I: Identify Basins in Voltage-Drop Landscape

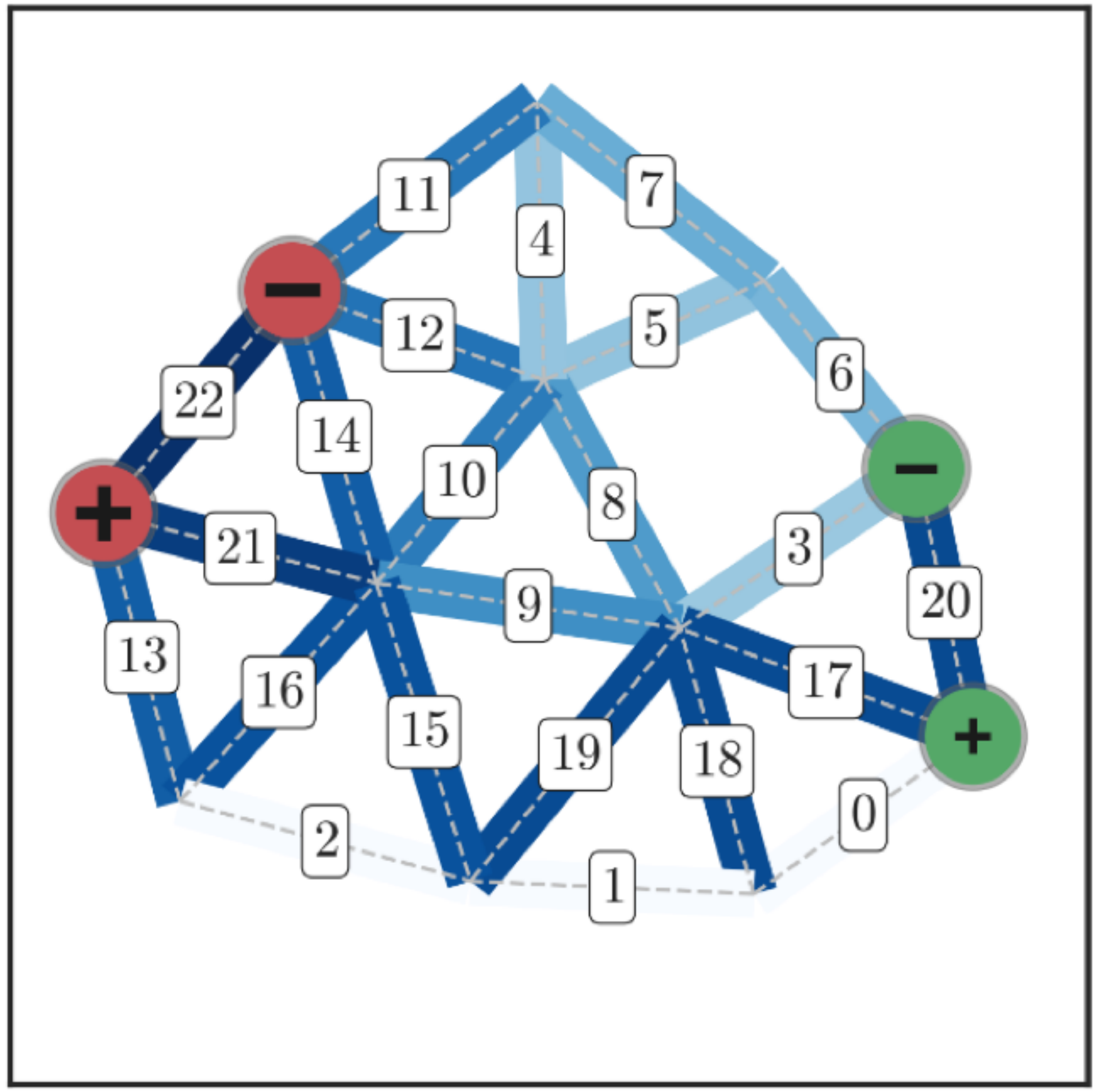


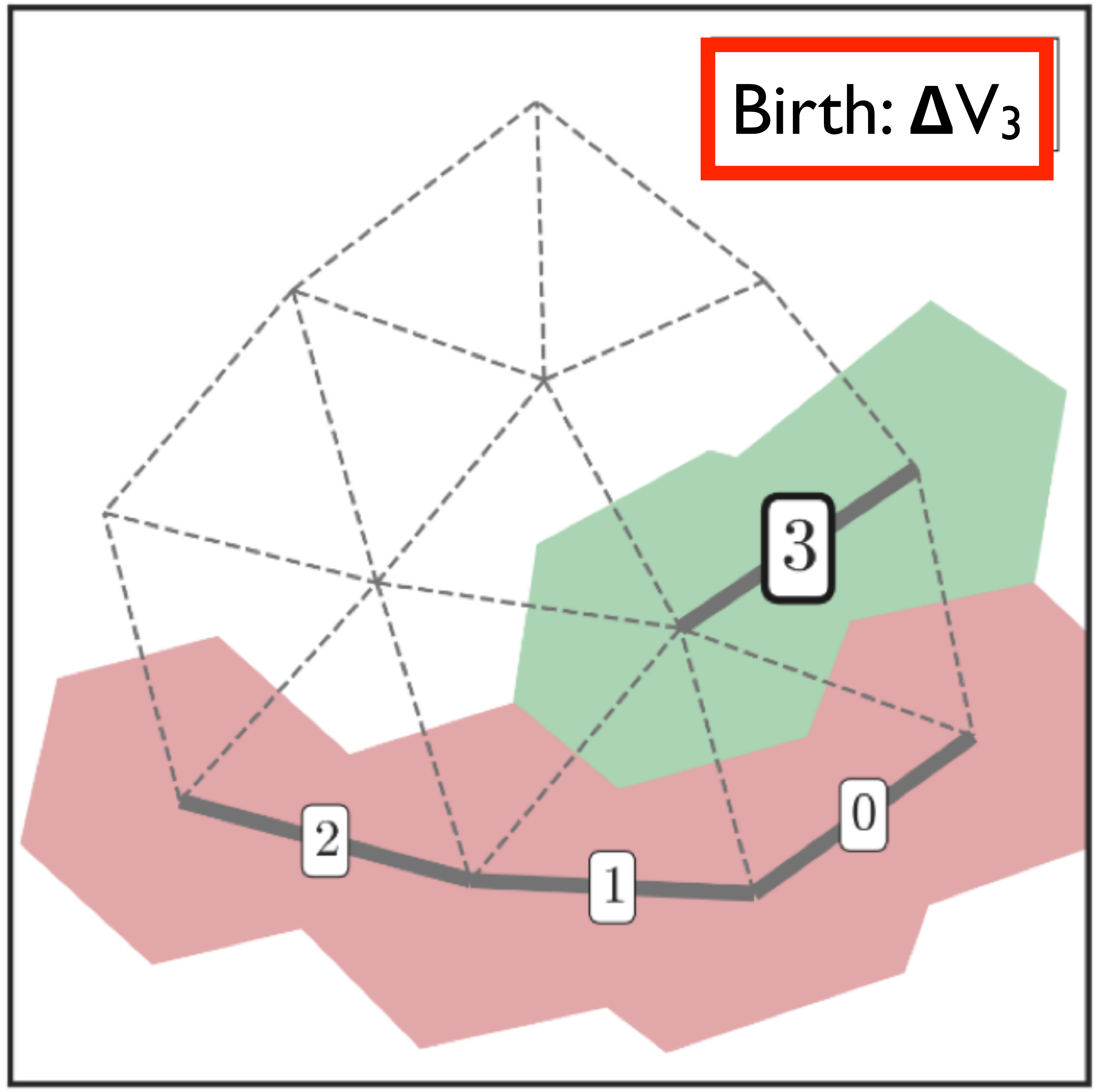


- Increase voltage drop and add edge as you reach the voltage drop across the edge
- Register appearance of new basin as “birth” of basin
- Connected components (0 Betti number)

Rocks, Liu, Katifori PRL 2021
Rocks, Liu, Katifori PRR 2020

Step I: Identify Basins in Voltage-Drop Landscape





- Increase voltage drop and add edge as you reach the voltage drop across the edge
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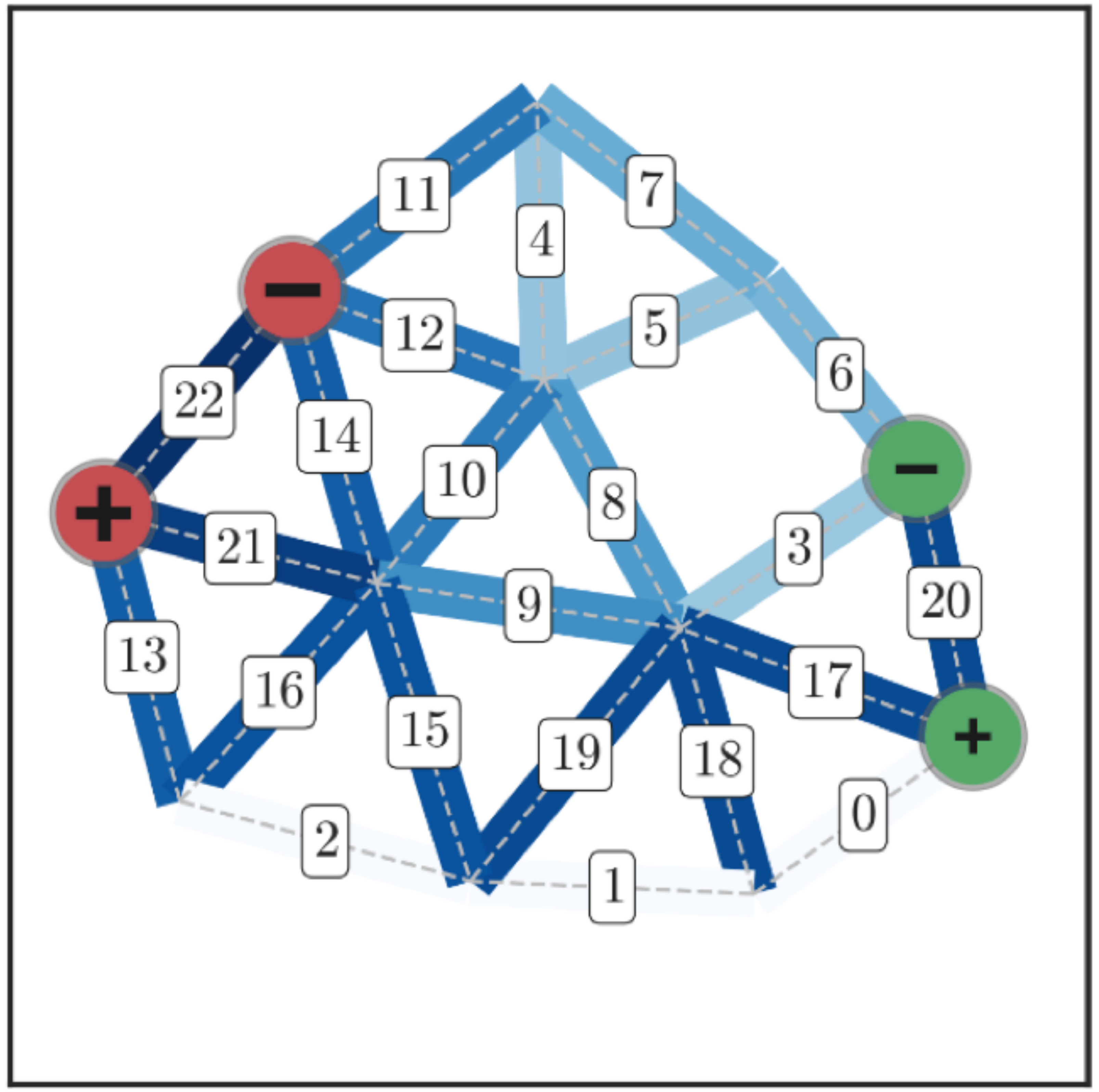
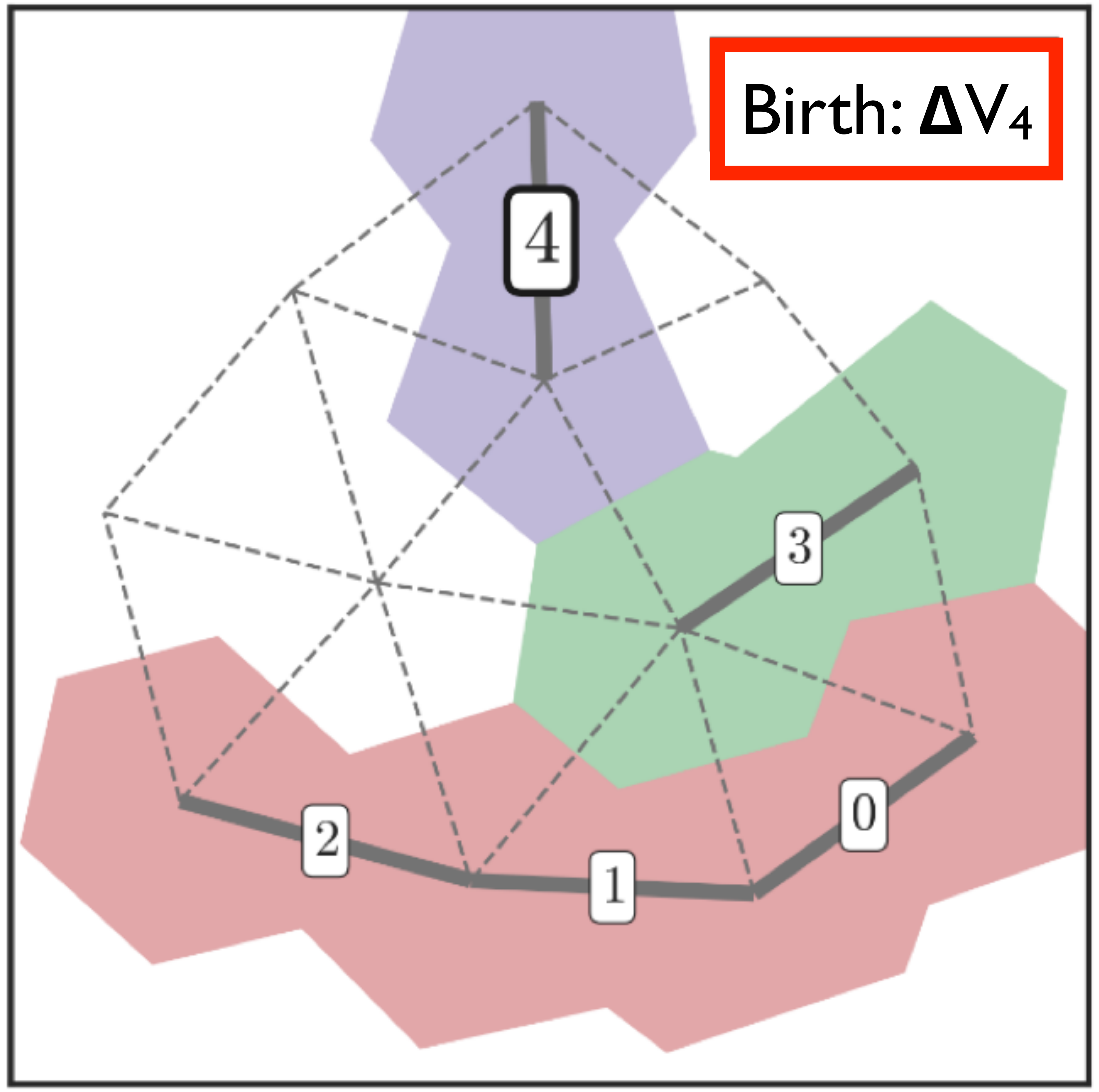
Rocks, Liu, Katifori PRL 2021
Rocks, Liu, Katifori PRR 2020

Step I: Identify Basins in Voltage-Drop Landscape





- Increase voltage drop and add edge as you reach the voltage drop across the edge
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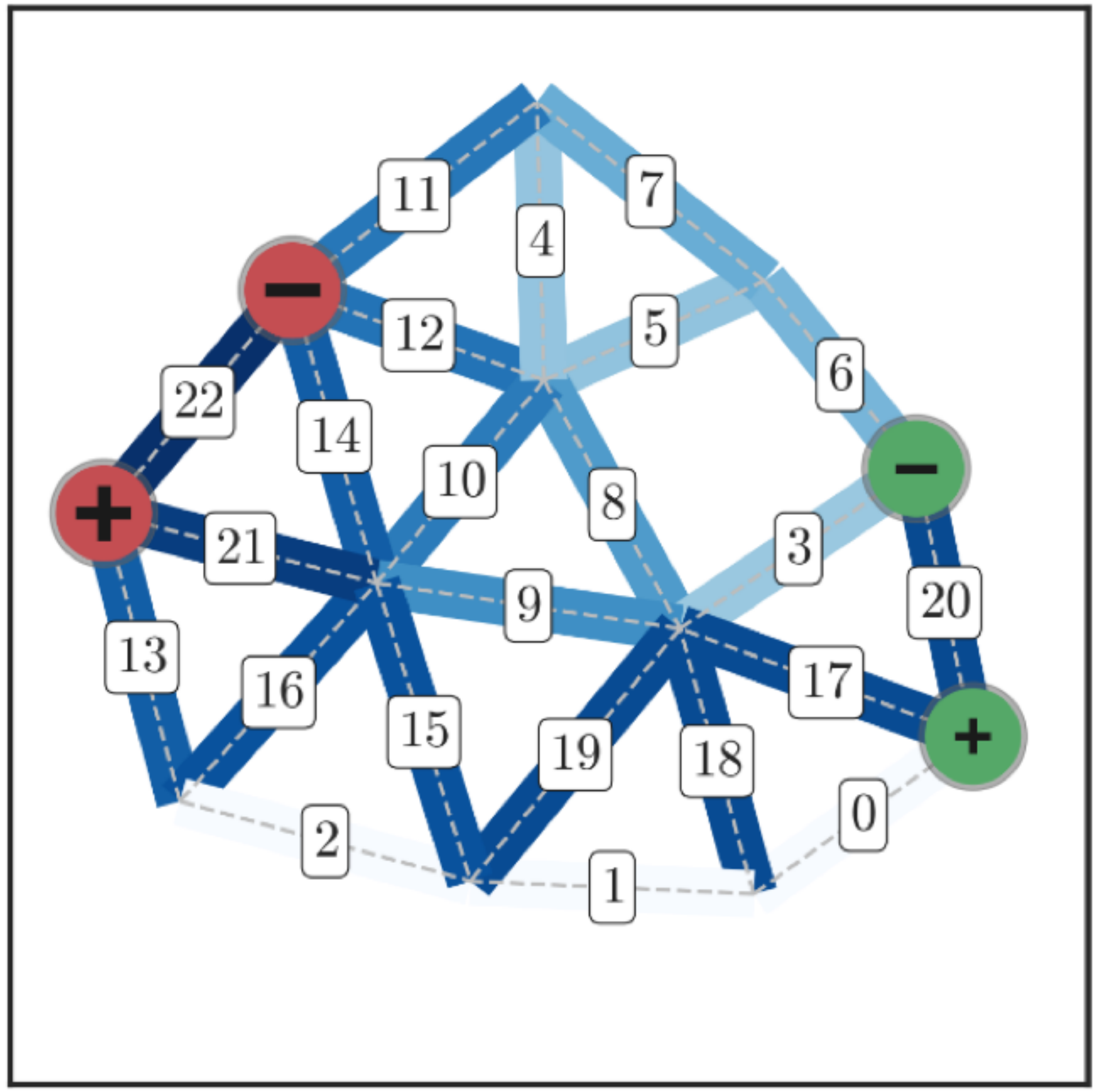
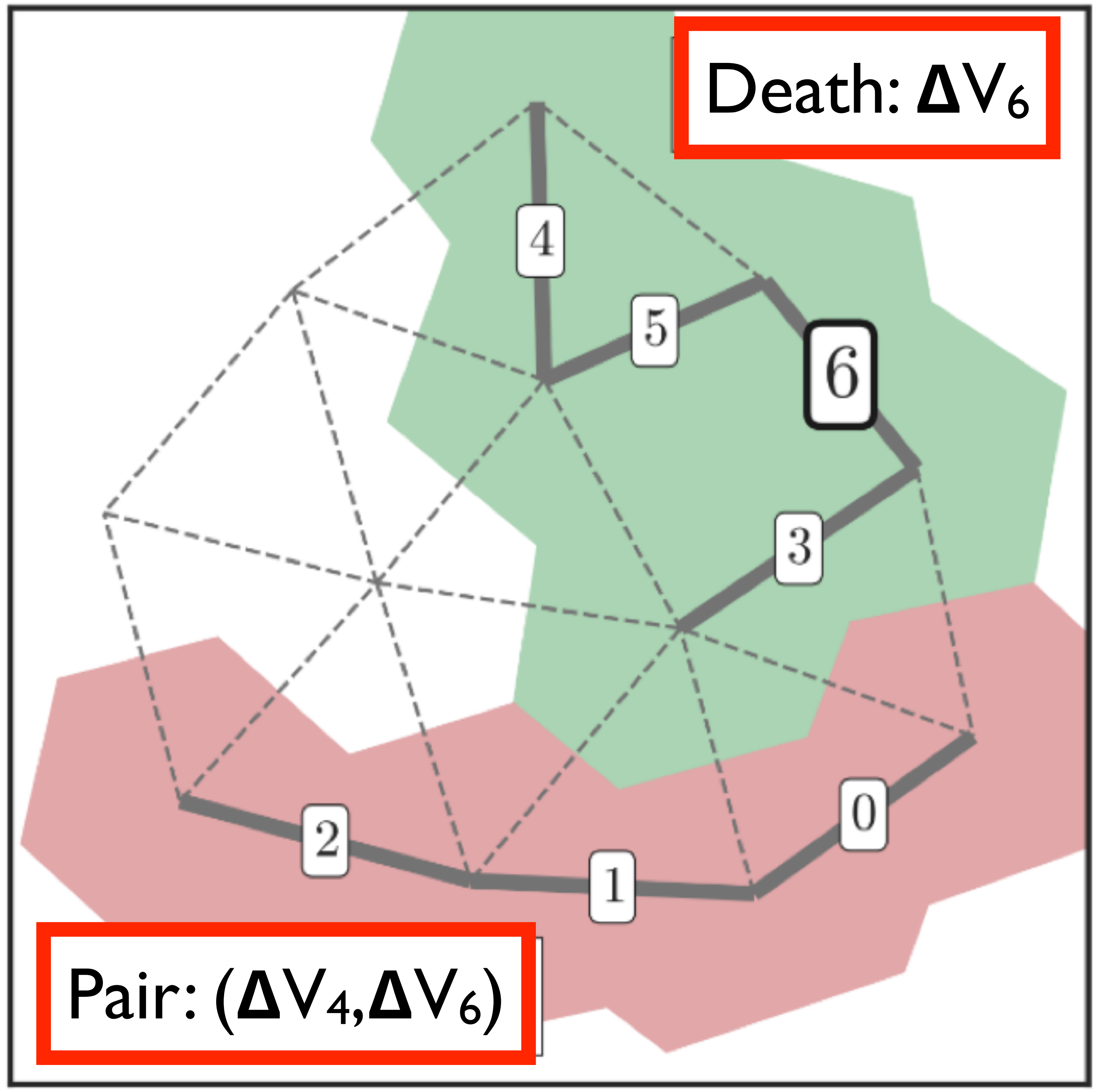
Rocks, Liu, Katifori PRL 2021
Rocks, Liu, Katifori PRR 2020

Step I: Identify Basins in Voltage-Drop Landscape

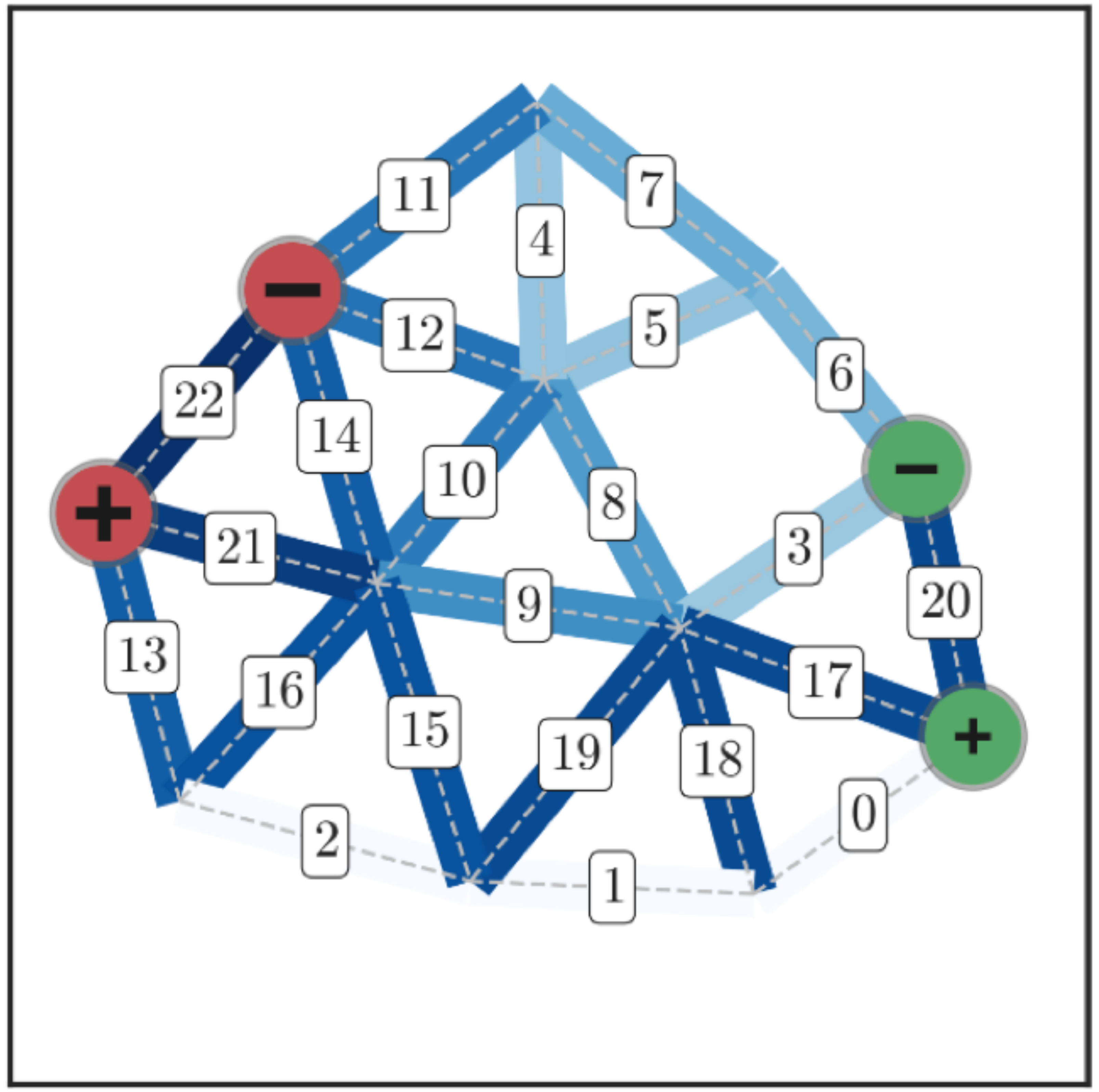


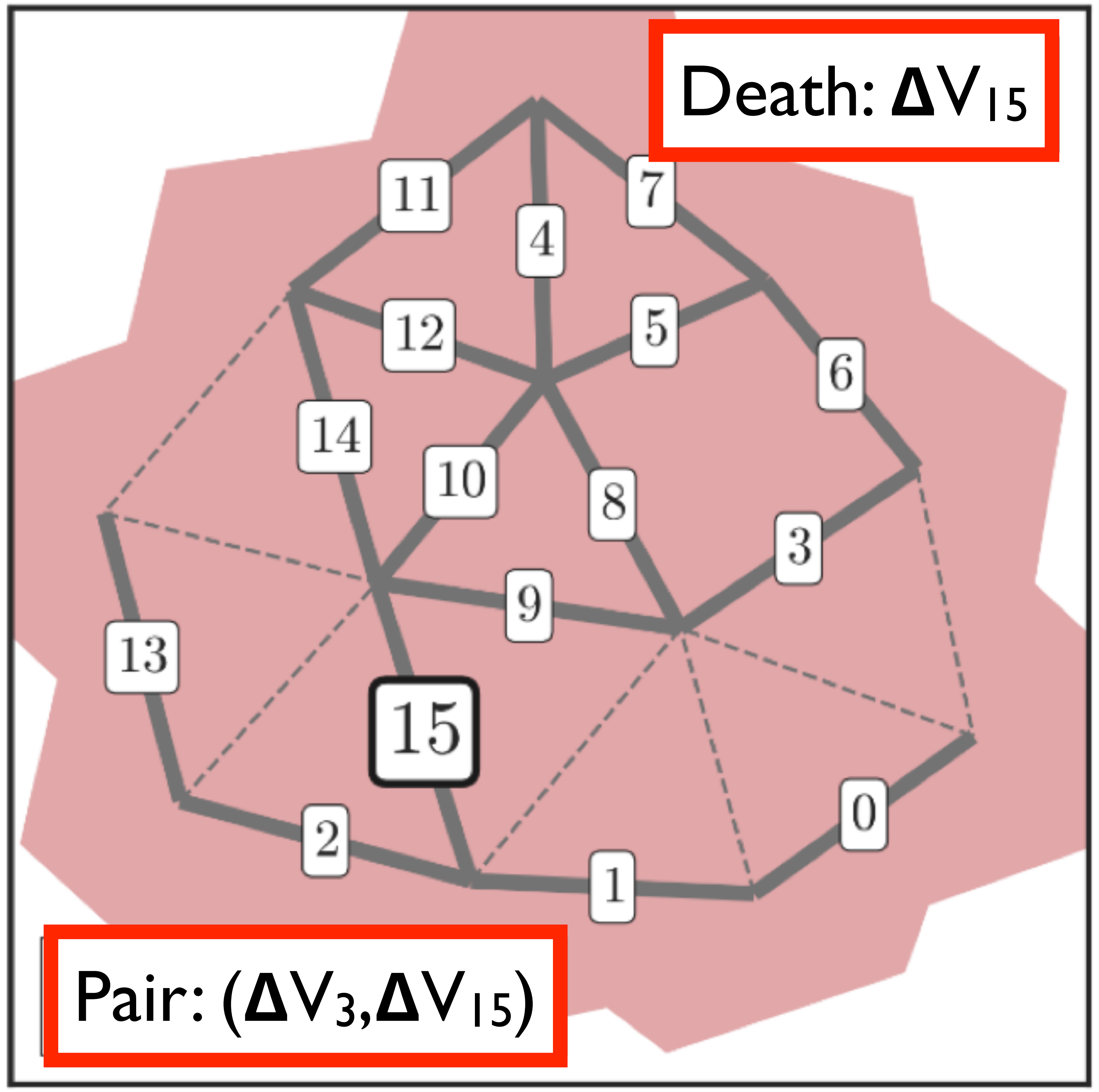


- Register merging of two basins into one when saddle is reached as "death" of younger basin

Rocks, Liu, Katifori PRL 2021
Rocks, Liu, Katifori PRR 2020

Step I: Identify Basins in Voltage-Drop Landscape





- Register merging of two basins into one when saddle is reached as "death" of younger basin

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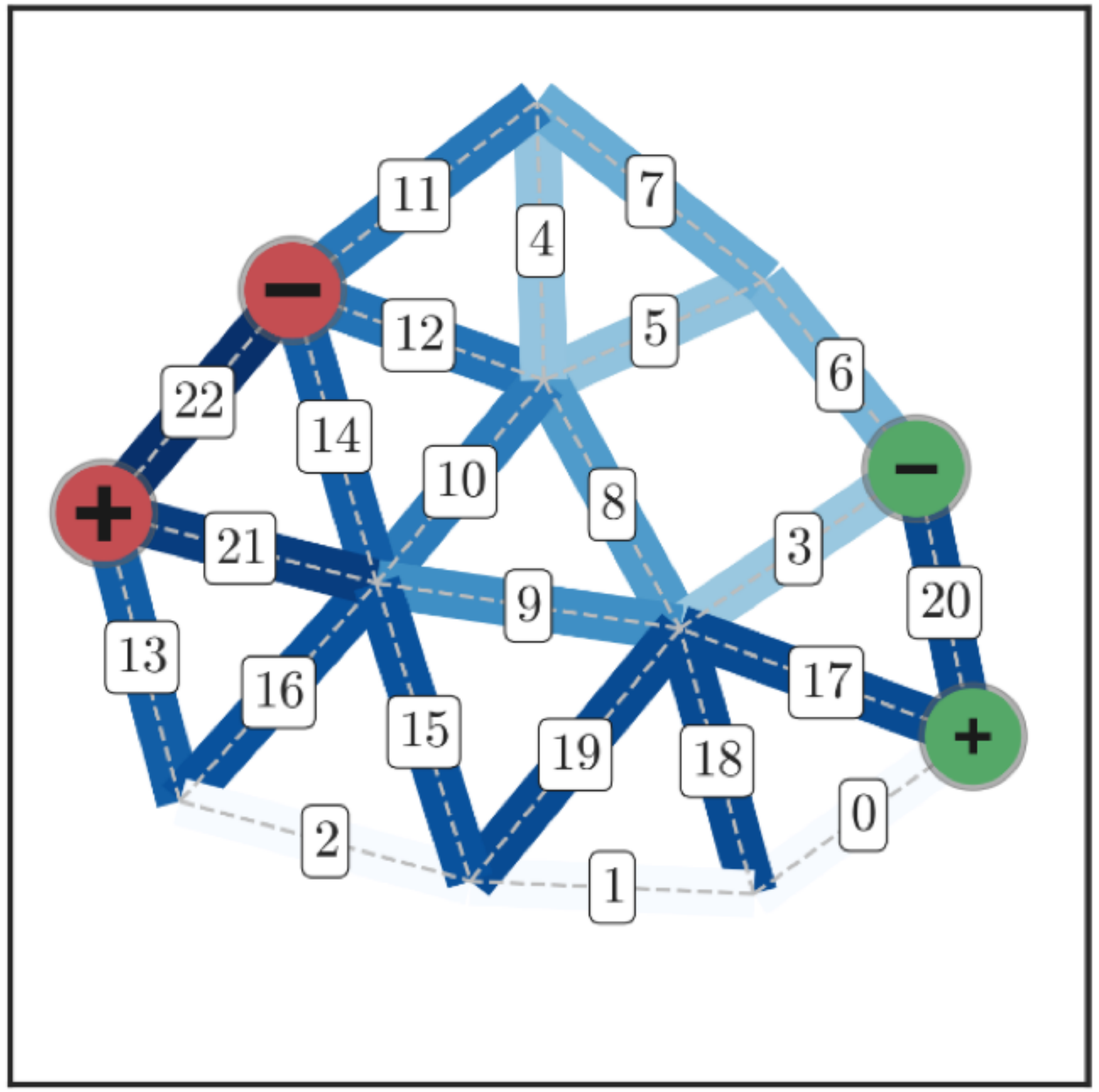
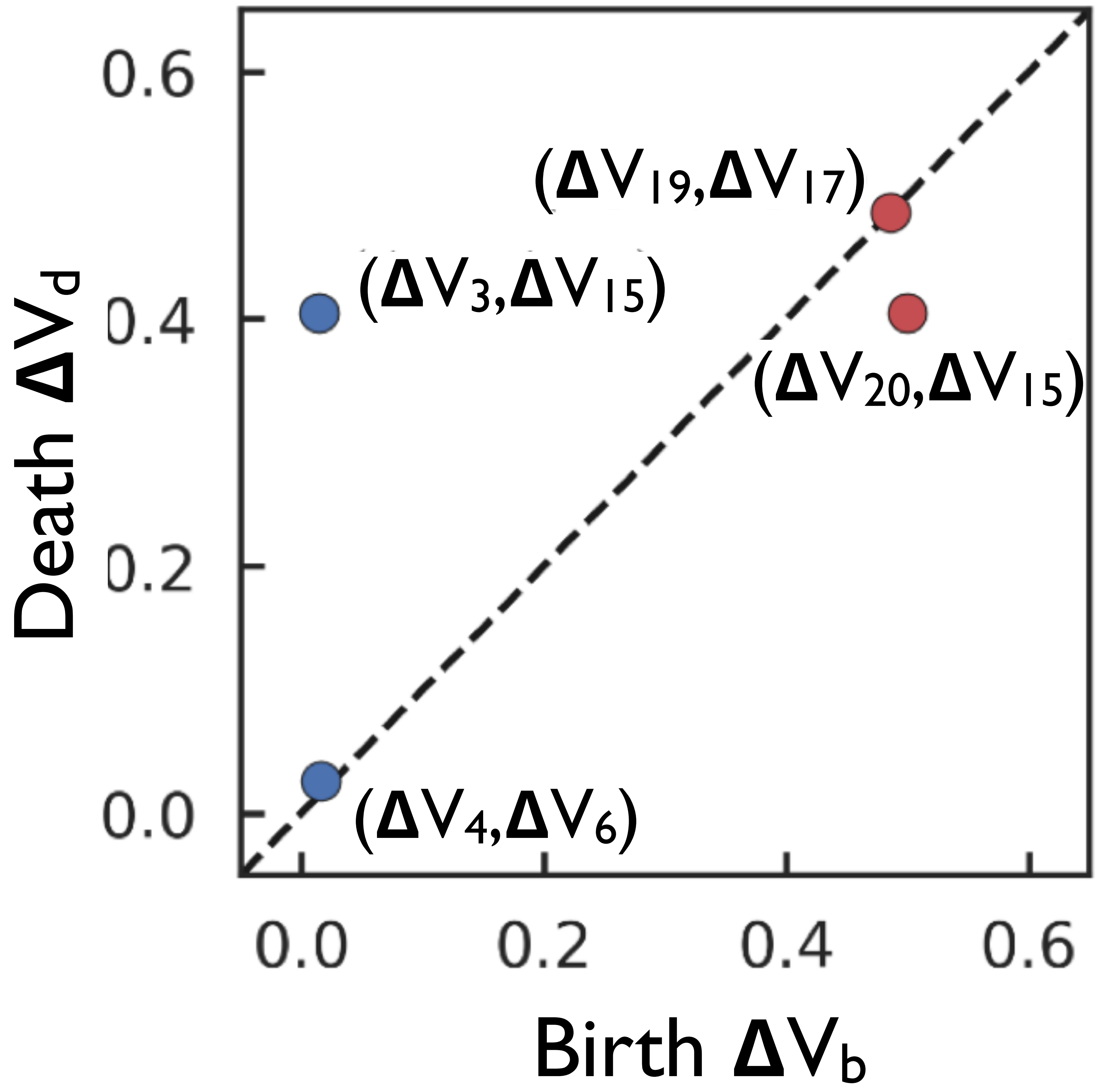
Persistent Homology Approach





- For each feature, plot death value of ΔV vs. birth value
- Small shallow basins in landscape fall near diagonal
- "Persistent" features lie far from diagonal

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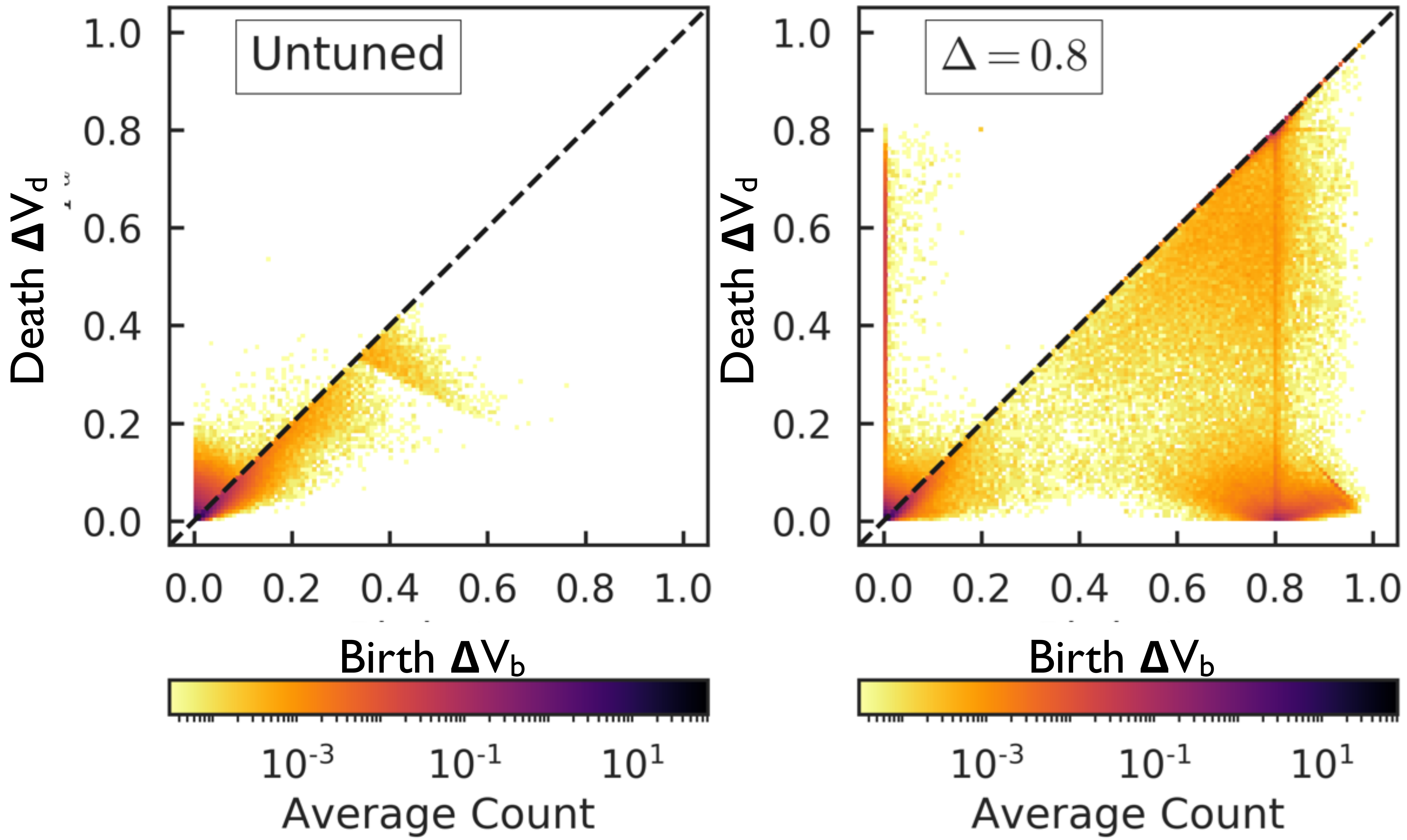
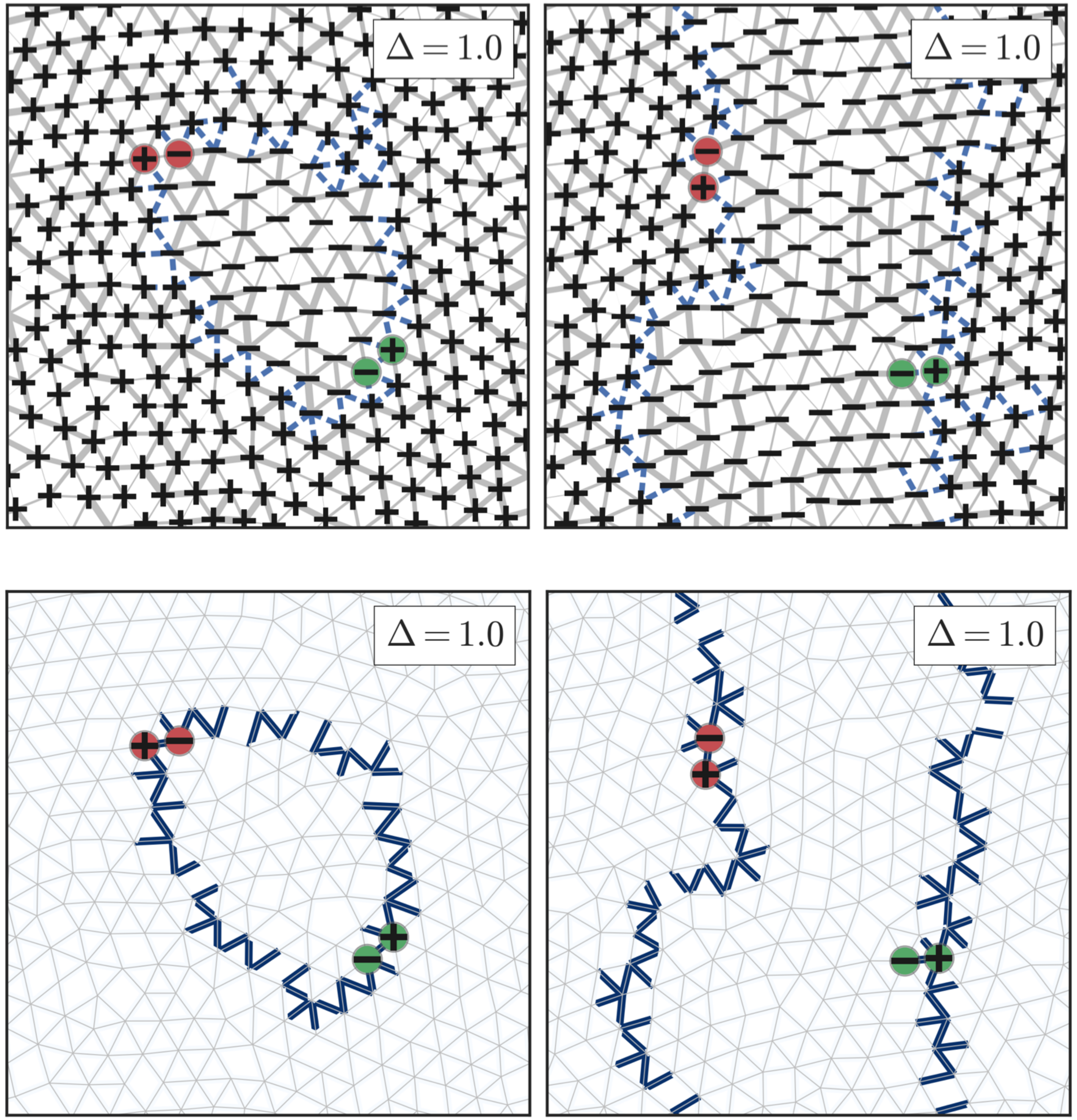
Effect of Tuning on *Ensemble Heat Map* Persistence Diagram



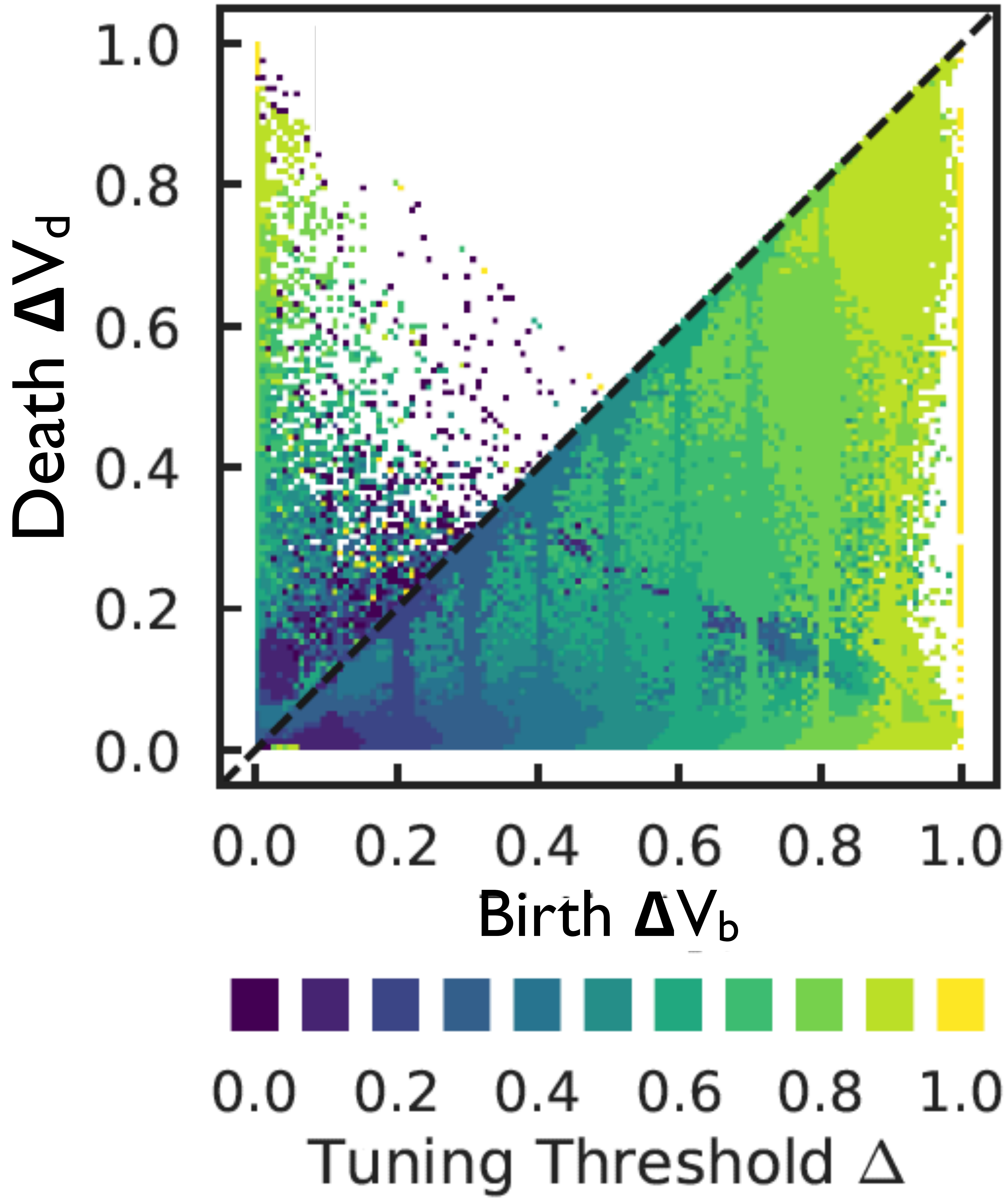
- Ascending: tuned networks have many basins with ΔV_b=0 (uniform node pressures) that persist all the way up to Δ
- Descending: tuned networks have many inverted basins with ΔV_b= Δ ("cracks" that separate regions of approx uniform node voltage)

Effect of Tuning on Persistence Diagram

- Look at extreme case where **Δ**=1
- Ascending: tuned networks have many basins with Δp_b=0 (uniform node pressures) that persist all the way up to Δ
- Descending: tuned networks have many inverted basins with Δp_b= Δ (“cracks” of removed edges that separate regions of uniform pressure)



These Features Really Do Correlate with Δ



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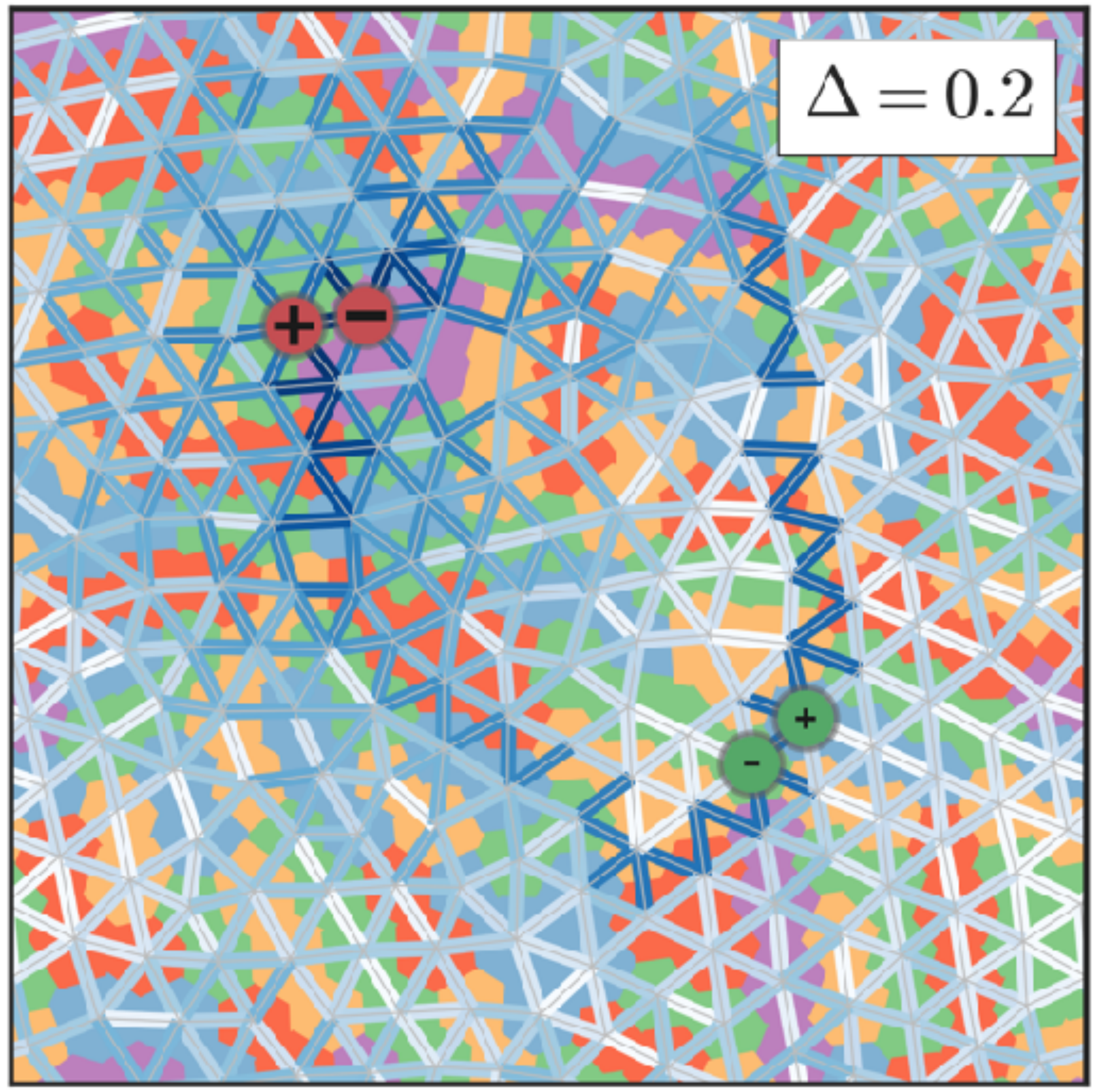
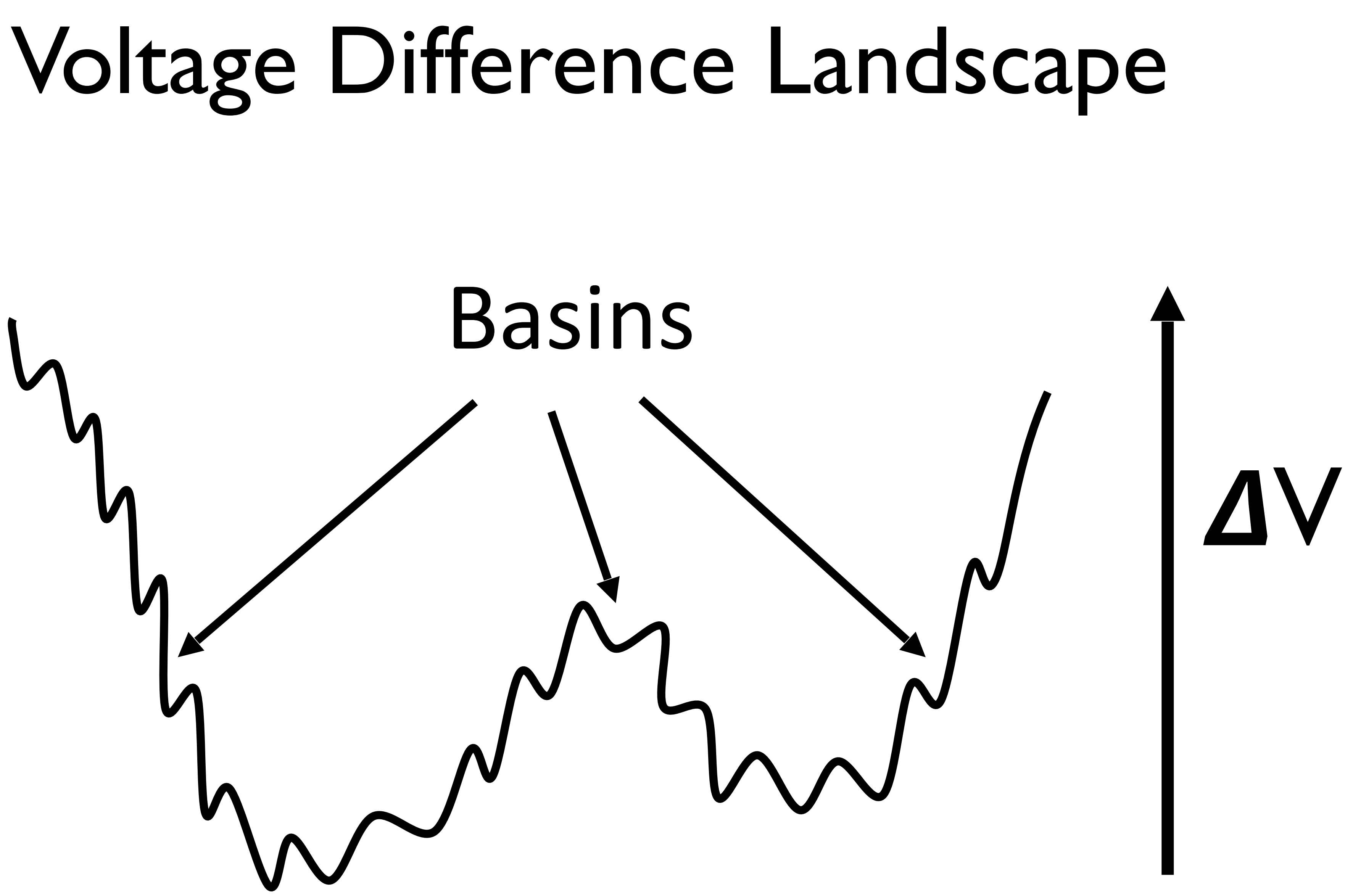
Problem: Too Many Basins!





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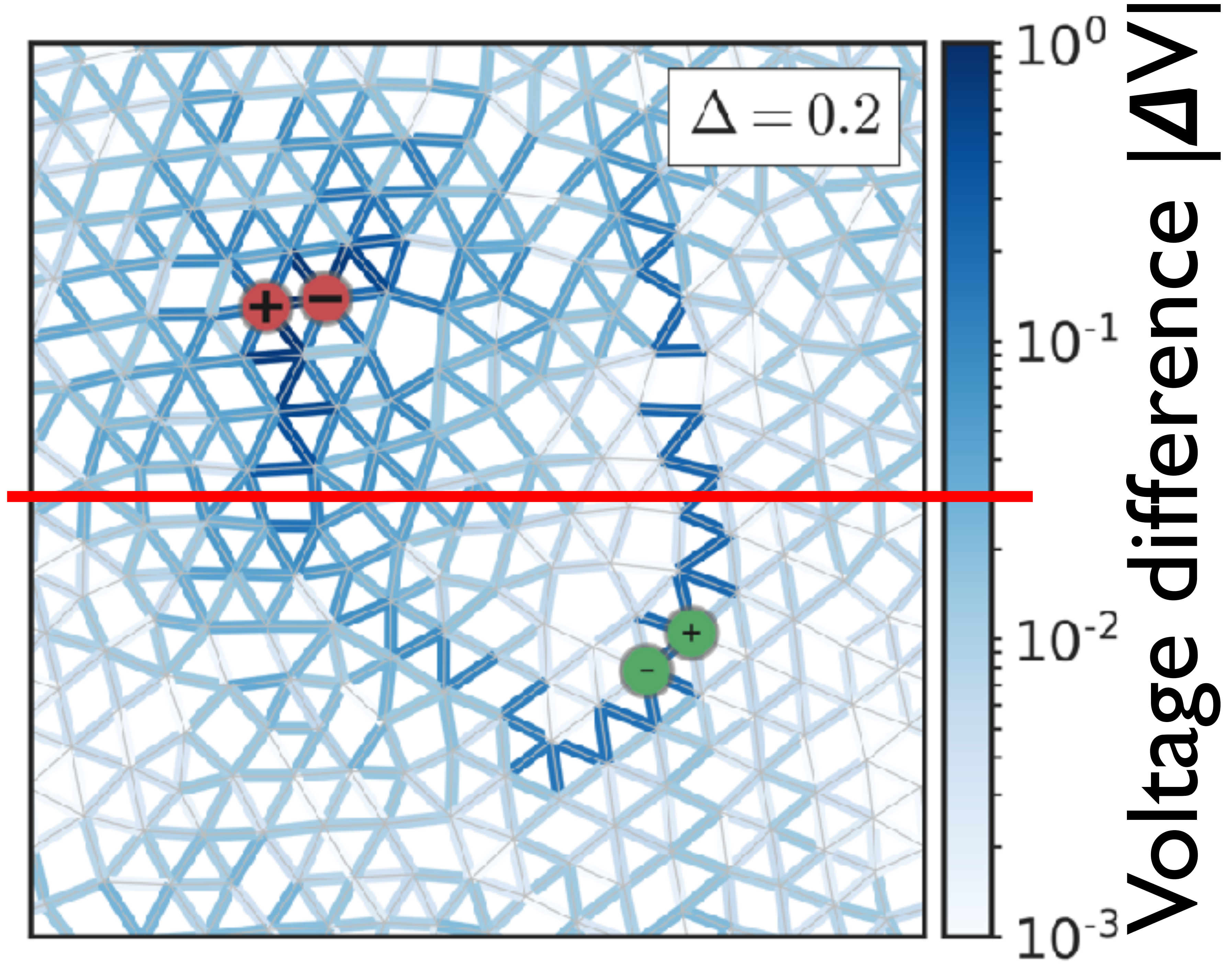
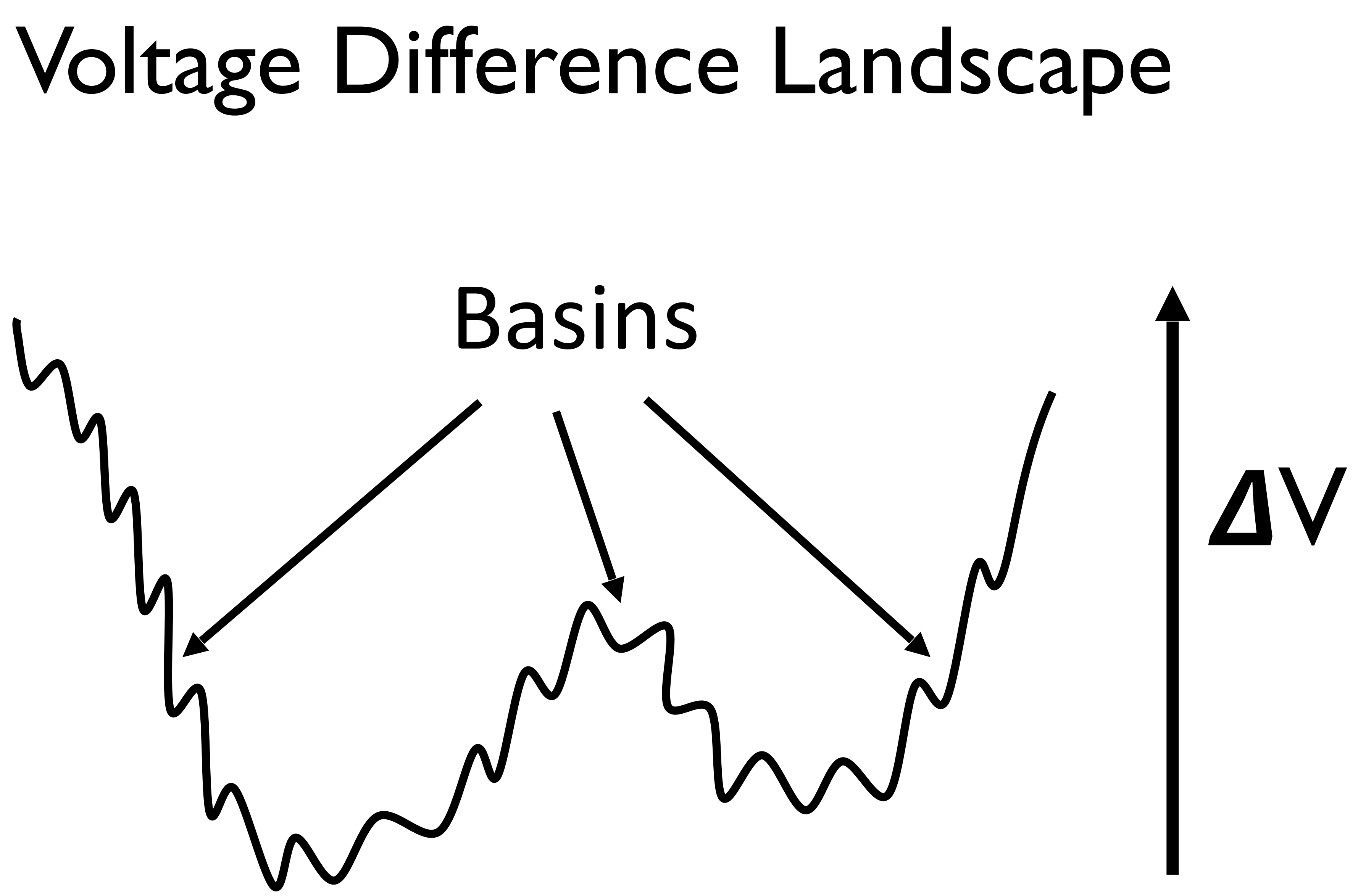
Step 0: Look at Voltage Difference Landscape





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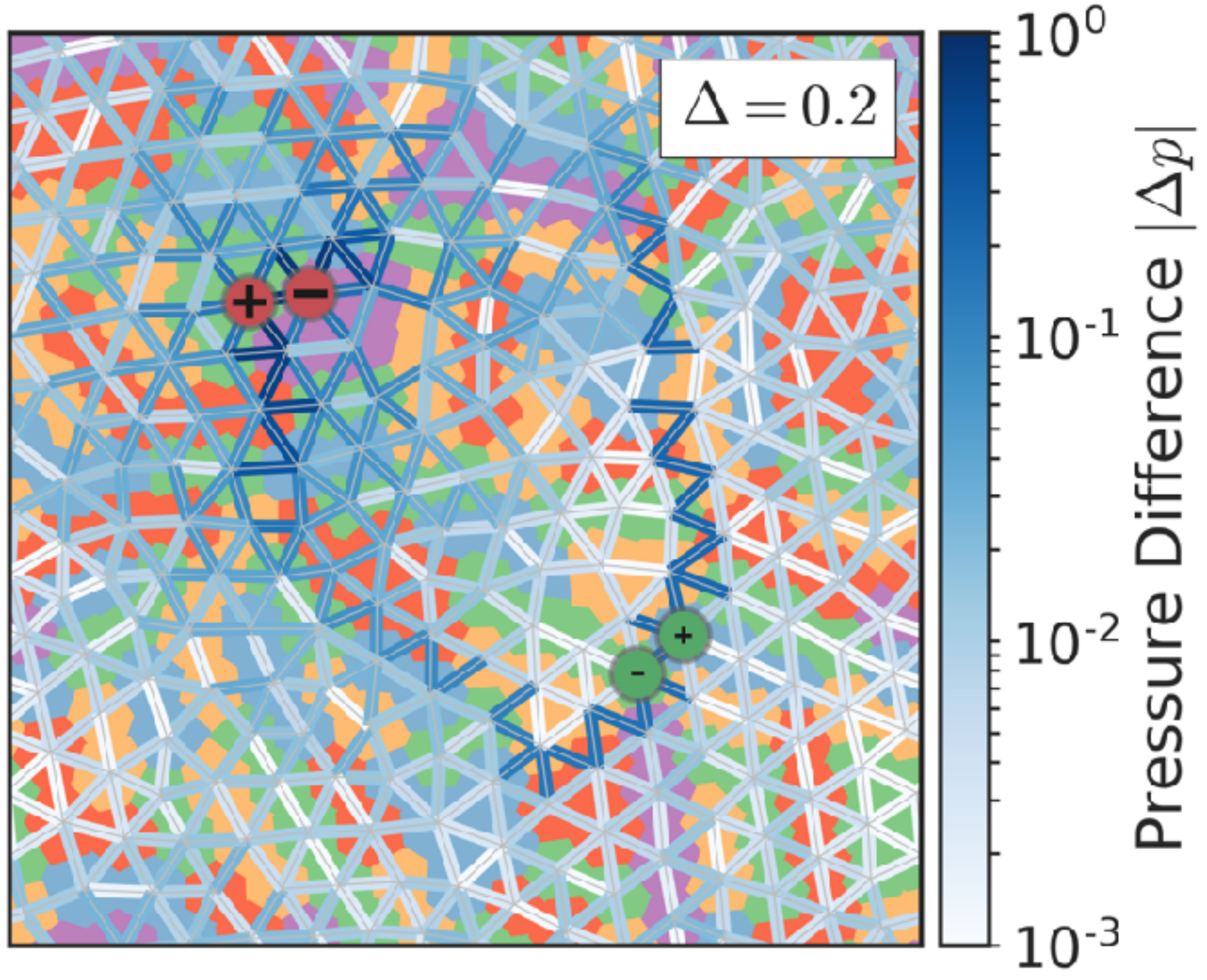
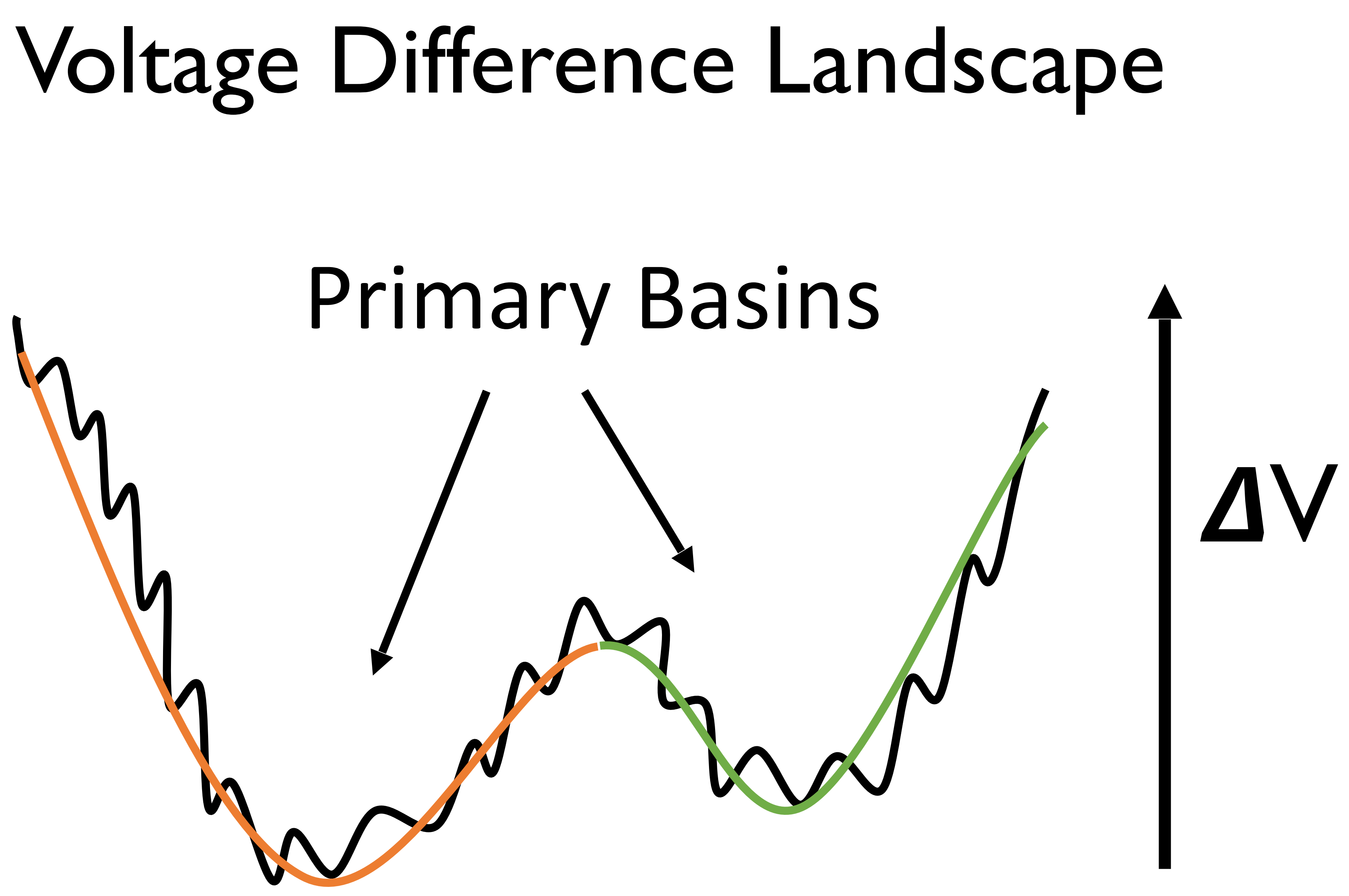
Step II: Coarse-Grain Landscape





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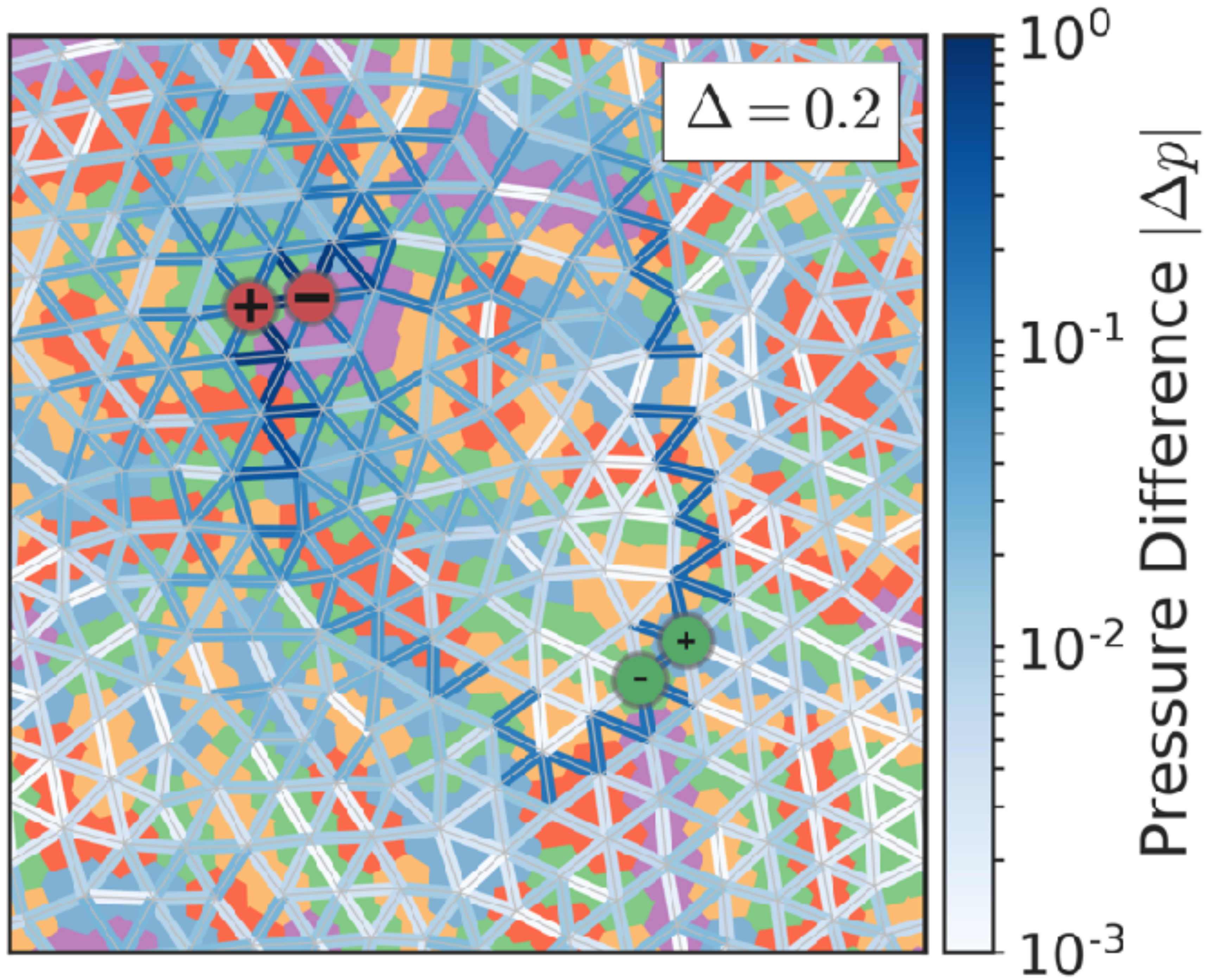
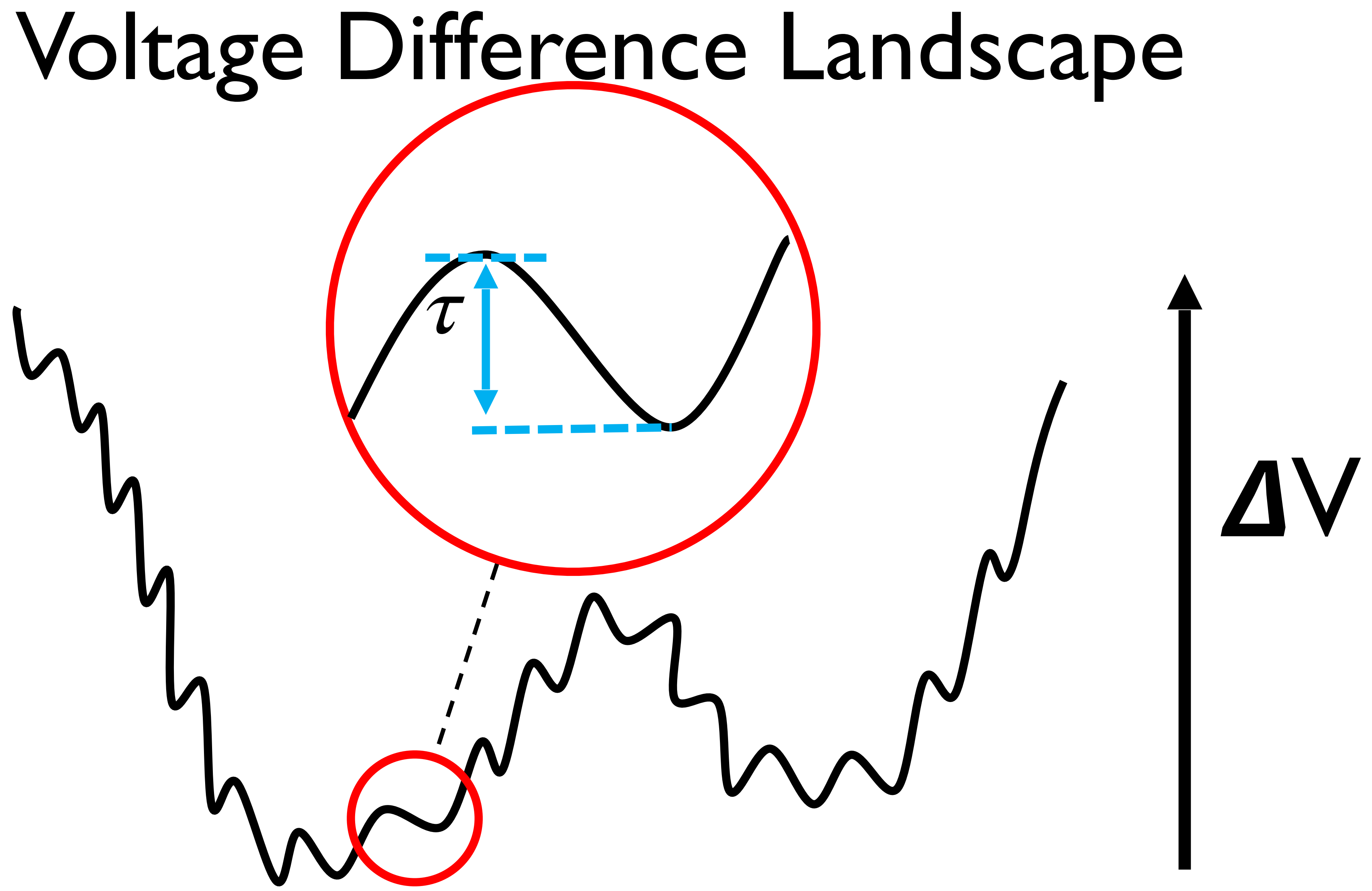
Step II: Coarse-Grain Landscape





Persistence (Significance)

Simplify in order of increasing τ (barrier height)

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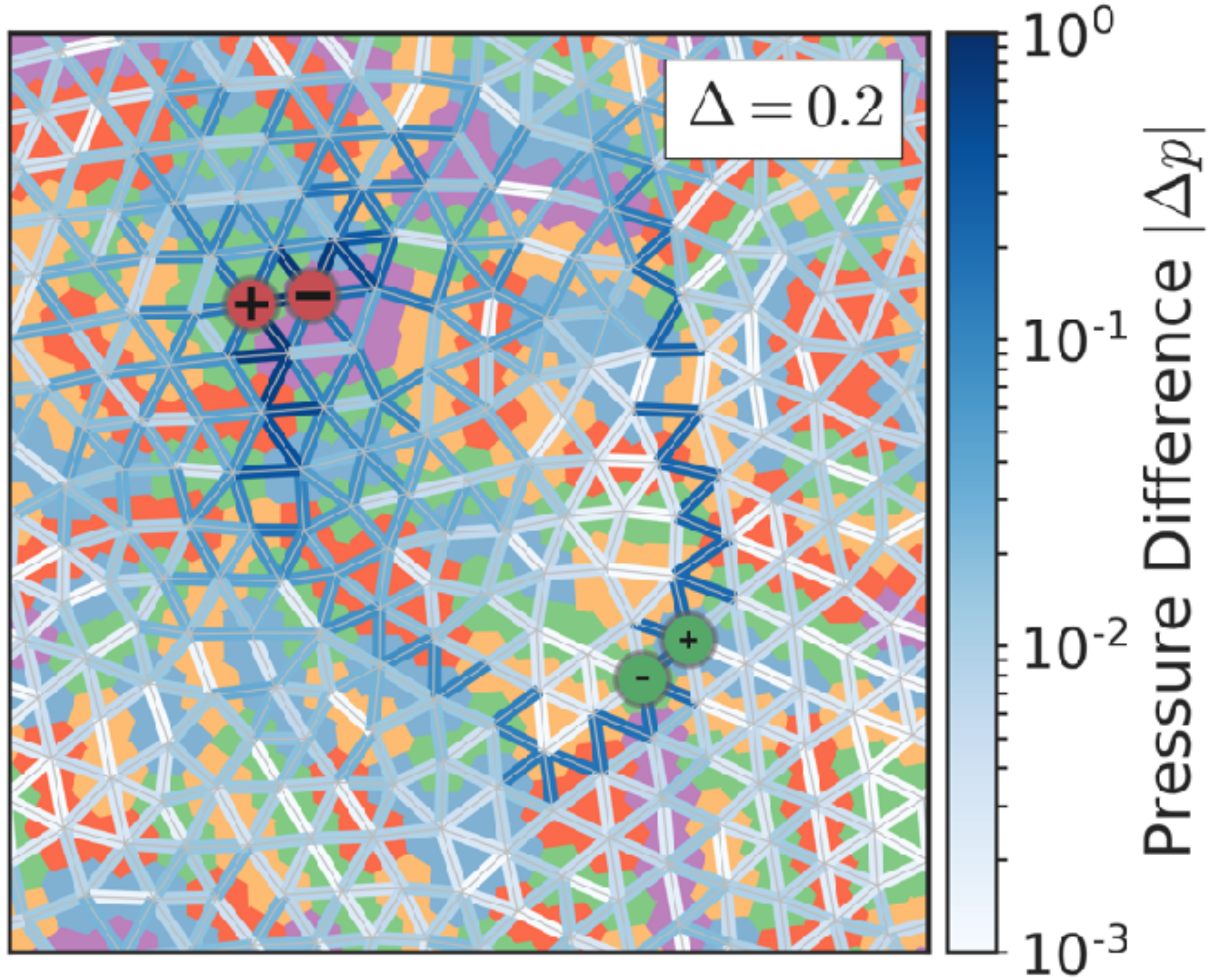
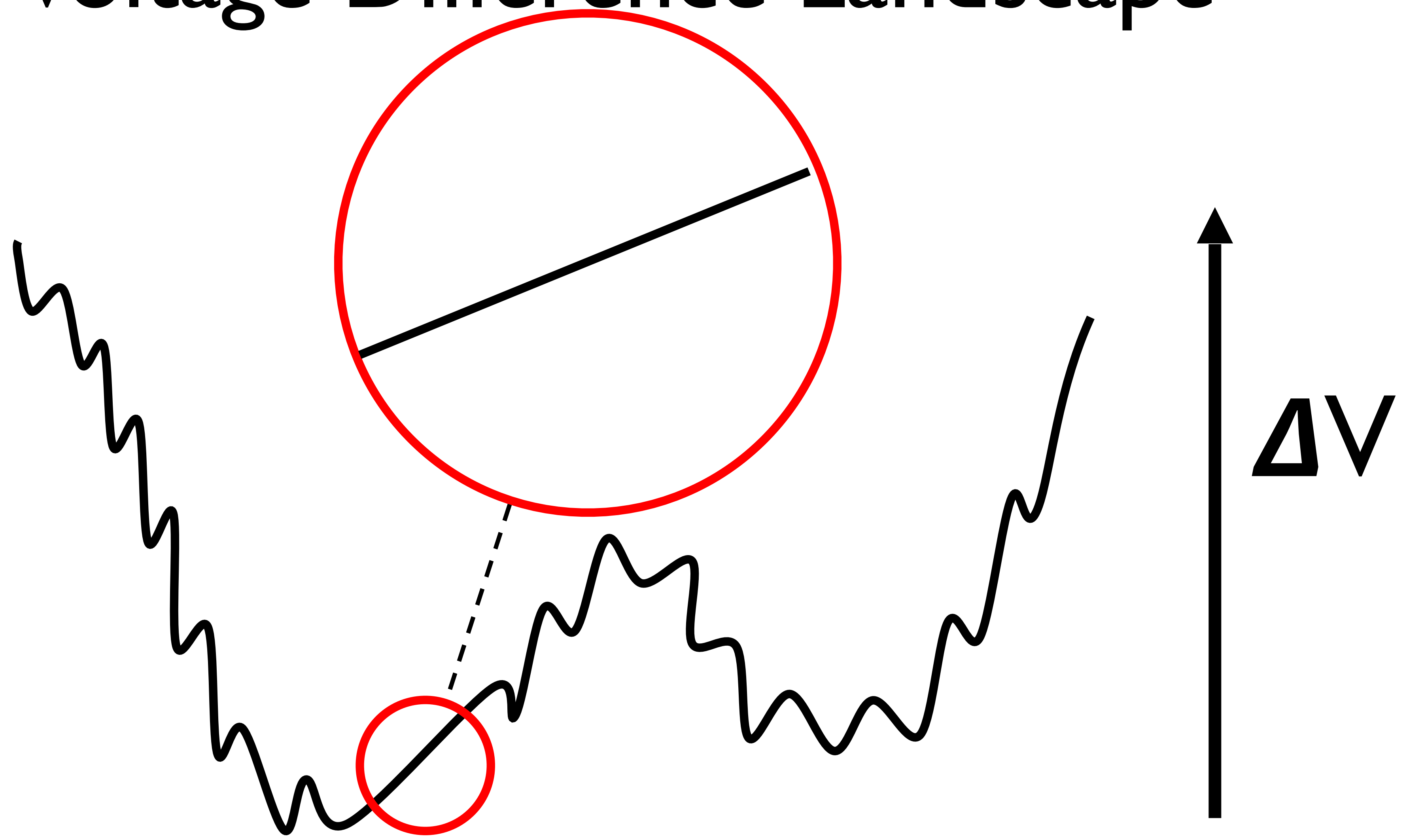
Step II: Coarse-Grain Landscape





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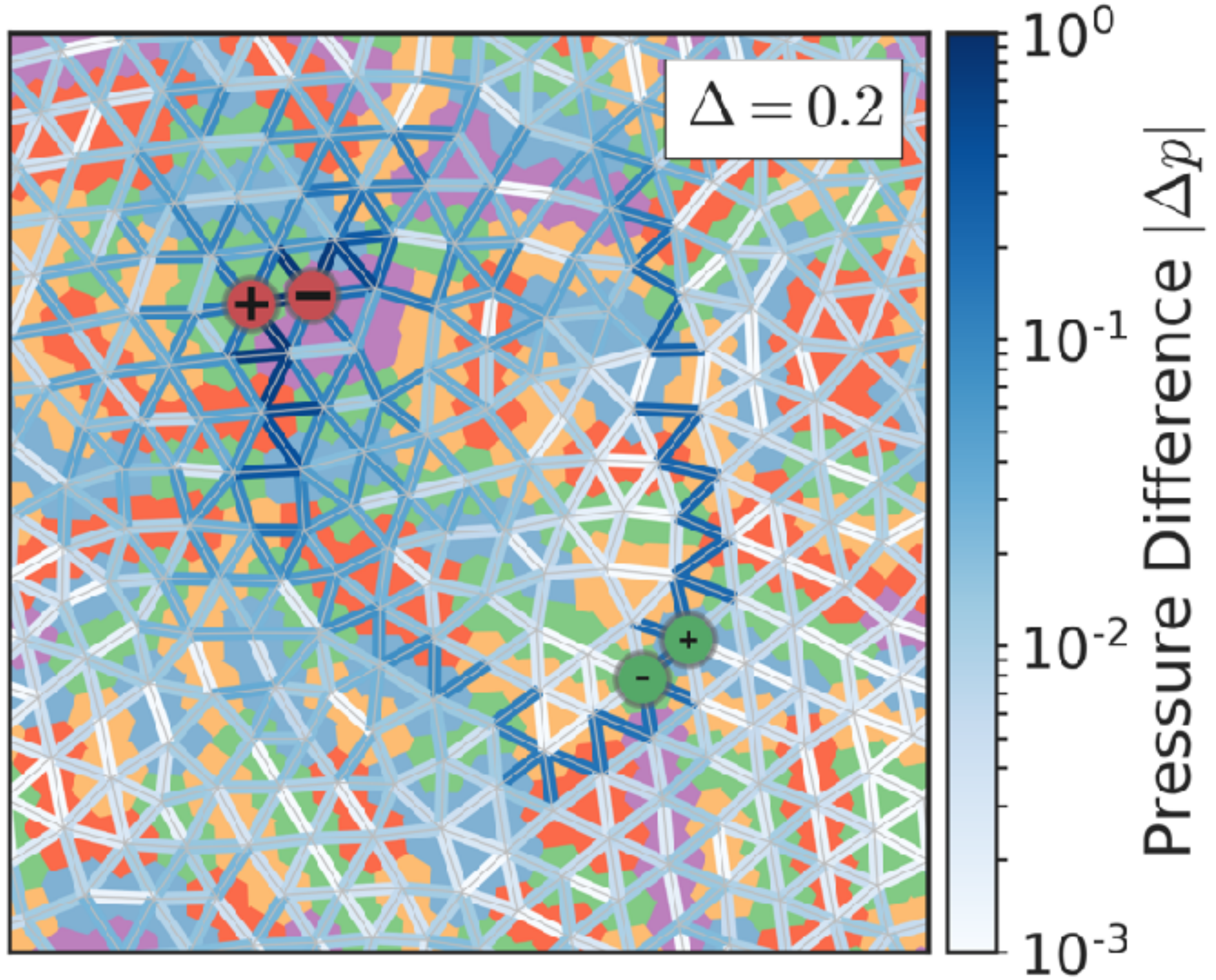
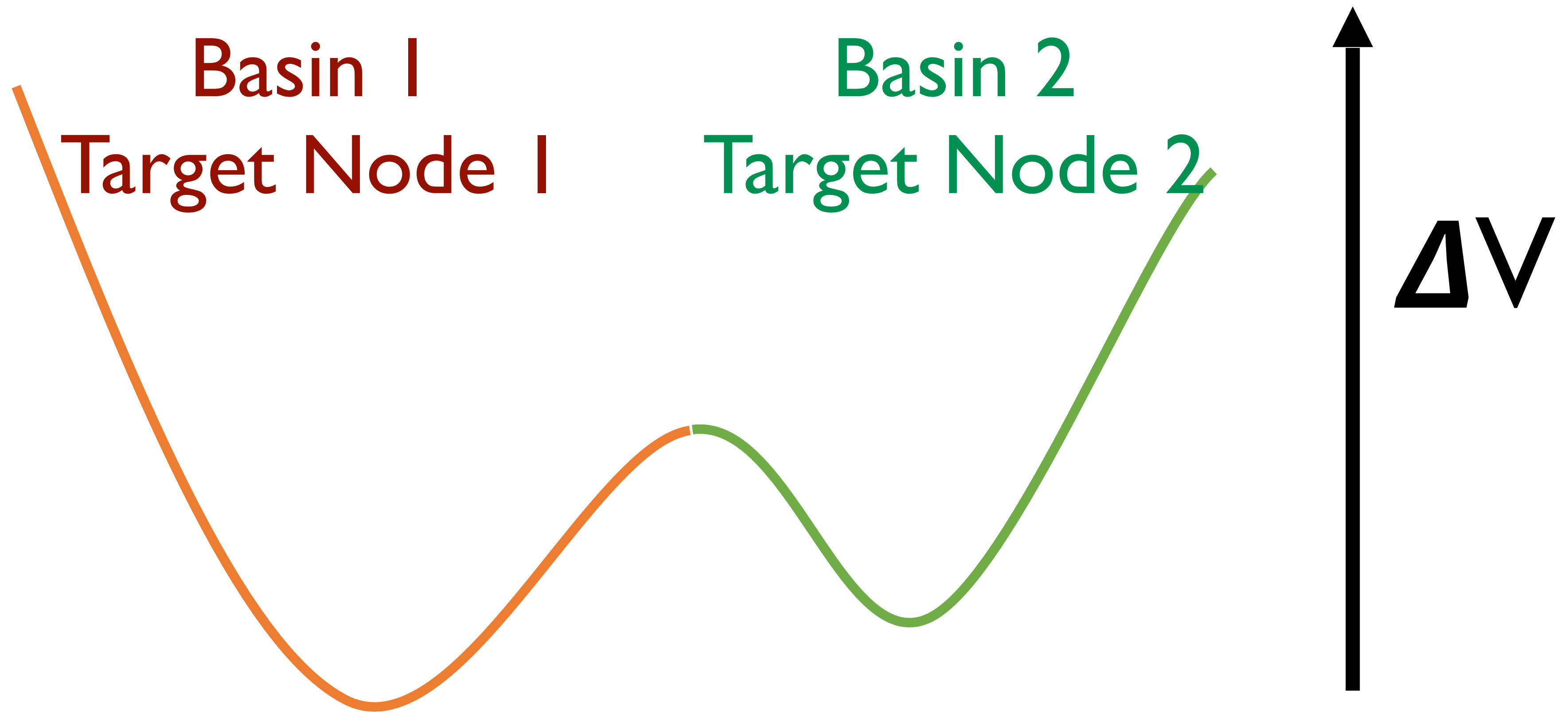


Voltage Difference Landscape



Persistence (Significance)

Simplify in order of increasing τ (barrier height)

Stop just before target nodes join same basin

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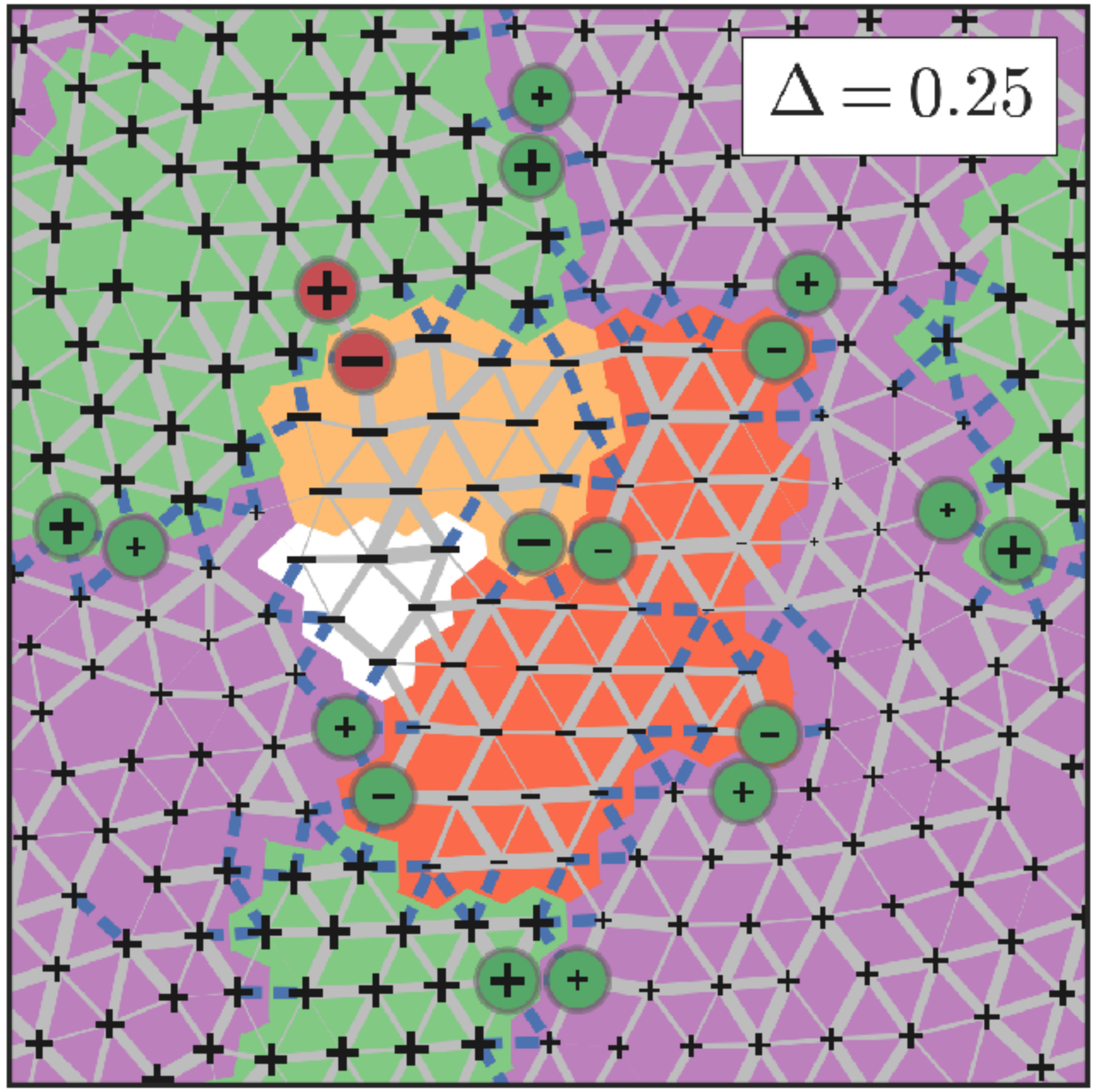
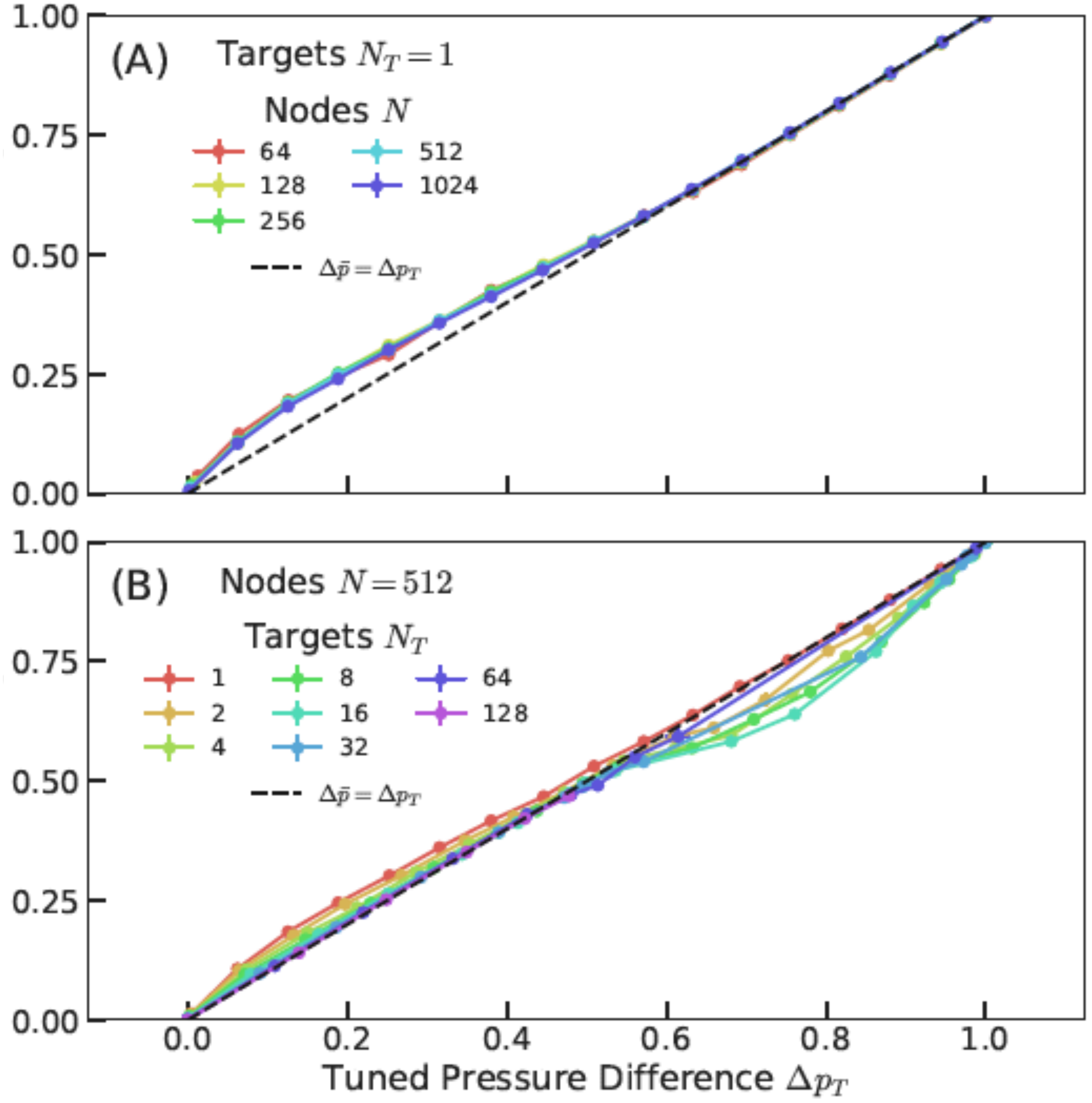
Persistent Homology Captures Function Quantitatively



mean sector voltage difference



tuned voltage drop

- Yes, it works!

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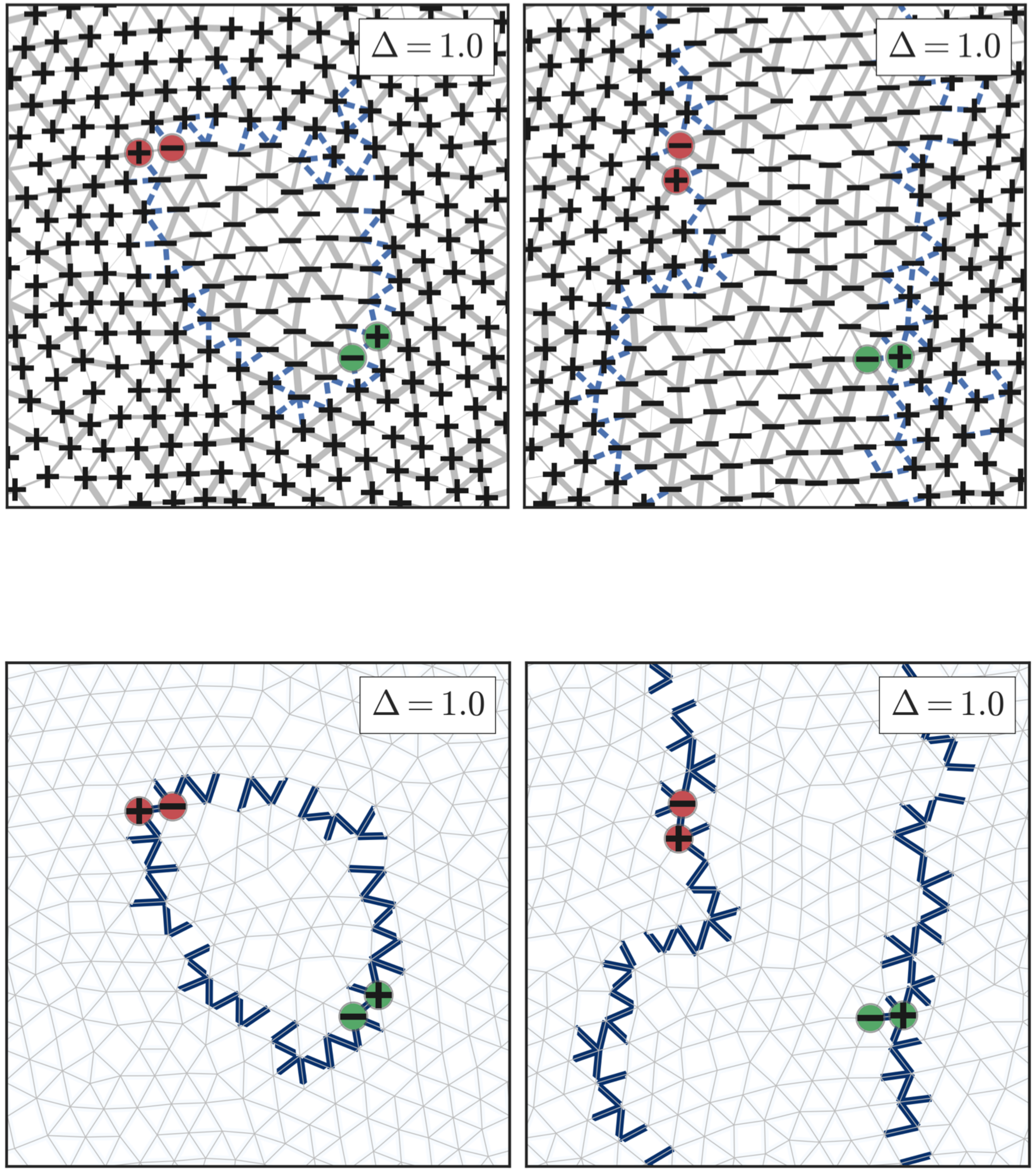
Electrical Networks vs Mechanical Networks

- In flow networks, sectors of nearly uniform node pressure or pathways of edges with nearly uniformly high pressure drops yield same information
- In mechanical networks, focus on local strain instead of pressure
- Unlike pressure, strain is defined over region not individual edges
- sectors of nearly uniform strain/pathways of nearly uniformly high strain do not yield same information



LRMSD Replaces Pressure/Voltage Difference

- Local root-mean-squared displacements measures deviation of node displacements in neighborhood with respect to rigid translations/rotations
- First define local deformation tensor $\hat{F}$ around node i that best describes nbrhood: $$\hat{F} = \left[\sum_j w_{ij}\left(\vec{b}_{ij} + \Delta\vec{u}_{ij}\right)\vec{b}_{ij}^T\right]\left[\sum_k w_{ik}\Delta\vec{b}_{ik}\vec{b}_{ik}^T\right]^{-1}$$
- Weights w_{ij} favor nodes j that are close to node i $w_{ij} = \dfrac{e^{-\frac{\ell_{ij}^2}{2\sigma^2}}\Theta(\ell_{\max} - \ell_{ij})(1-\delta_{ij})}{\sum_k e^{-\frac{\ell_{ik}^2}{2\sigma^2}}\Theta(\ell_{\max} - \ell_{ik})(1-\delta_{ik})}$
- $\hat{b}_{ij}$ is vector from node i to node j without source strain
- $\Delta\vec{u}_{ij}$ is displacement of node i from node j due to source strain
- $R = \hat{F}(\hat{F}^T\hat{F})^{-1/2}$ ~ local rigid-body rotation matrix
- LRMSD for node i $$\delta u_i = \sqrt{\sum_j w_{ij}\left[\Delta\vec{u}_{ij} - (R - I)\vec{b}_{ij}\right]^2}$$

GO TO SLIDES

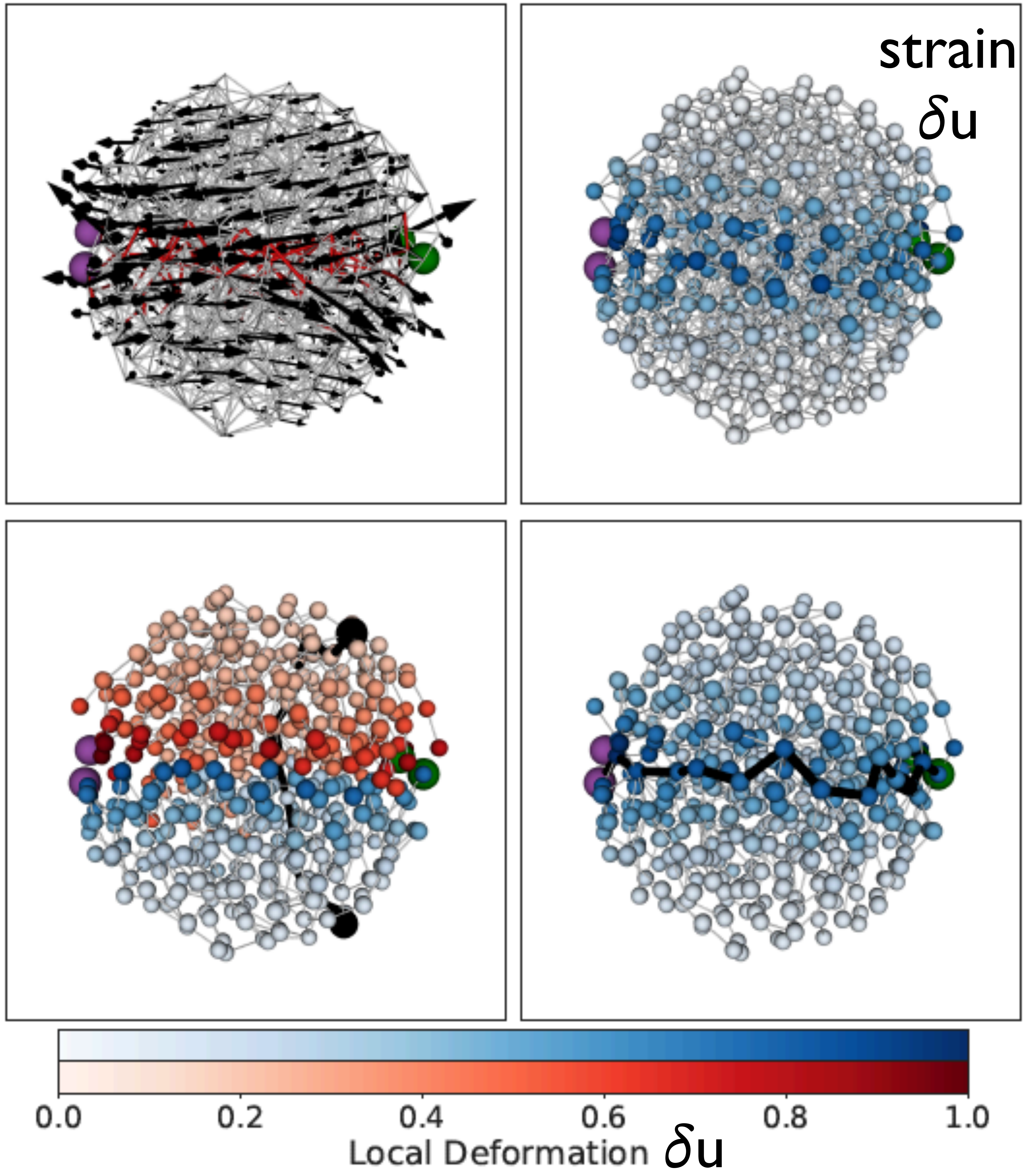
Hinge and Pathway Scales

Hinge pathway connects minimum δu within each sector with pathway of lowest δu

δu_h is max δu along pathway

δu^* is max δu at source/target nodes

$\delta u_h/\delta u^*$ quantifies significance of hinge sectors



Strain pathway is pathway of highest δu connecting source to target

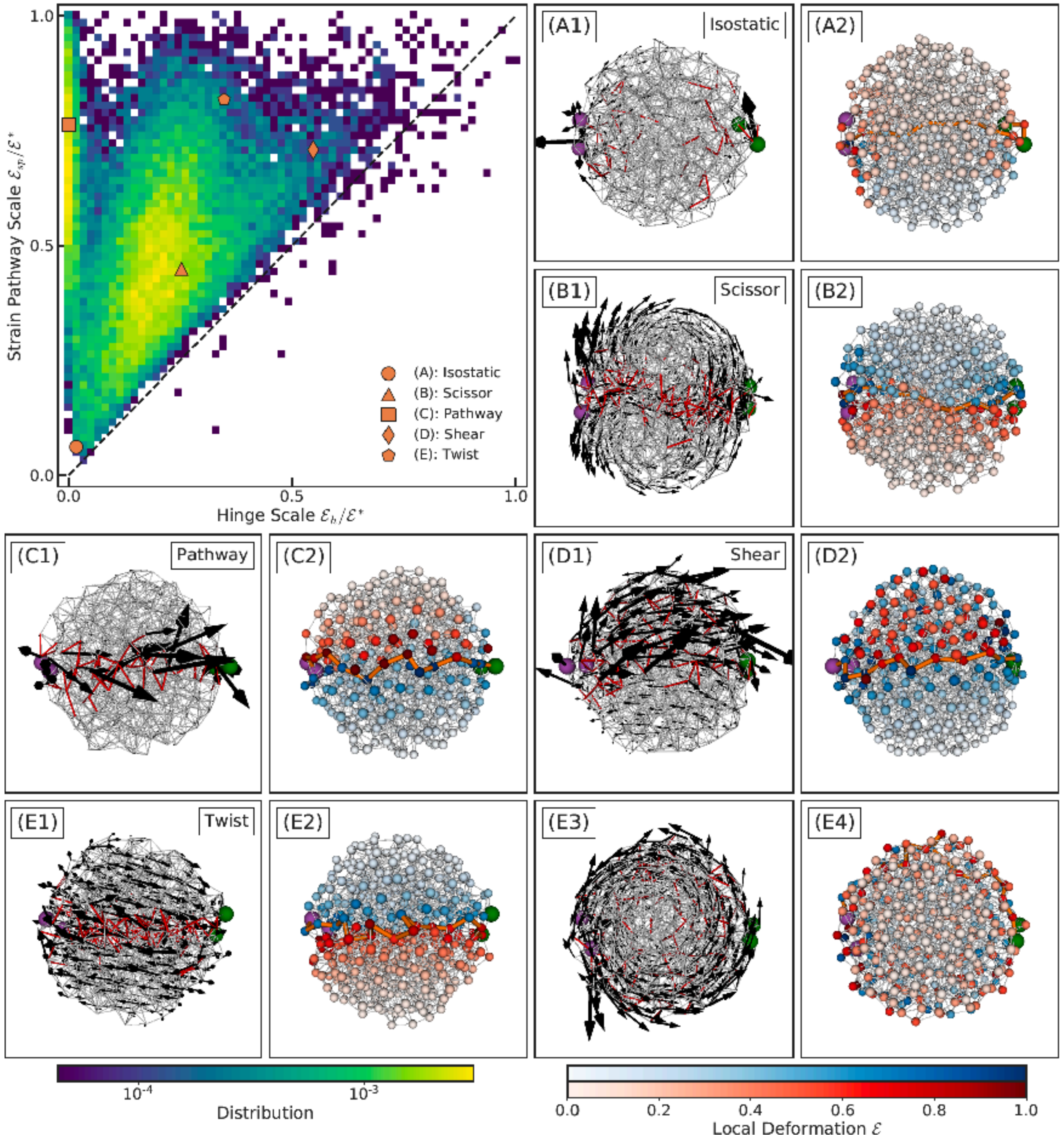
δu_{sp} is min δu along pathway

δu^* is max δu at source/target nodes

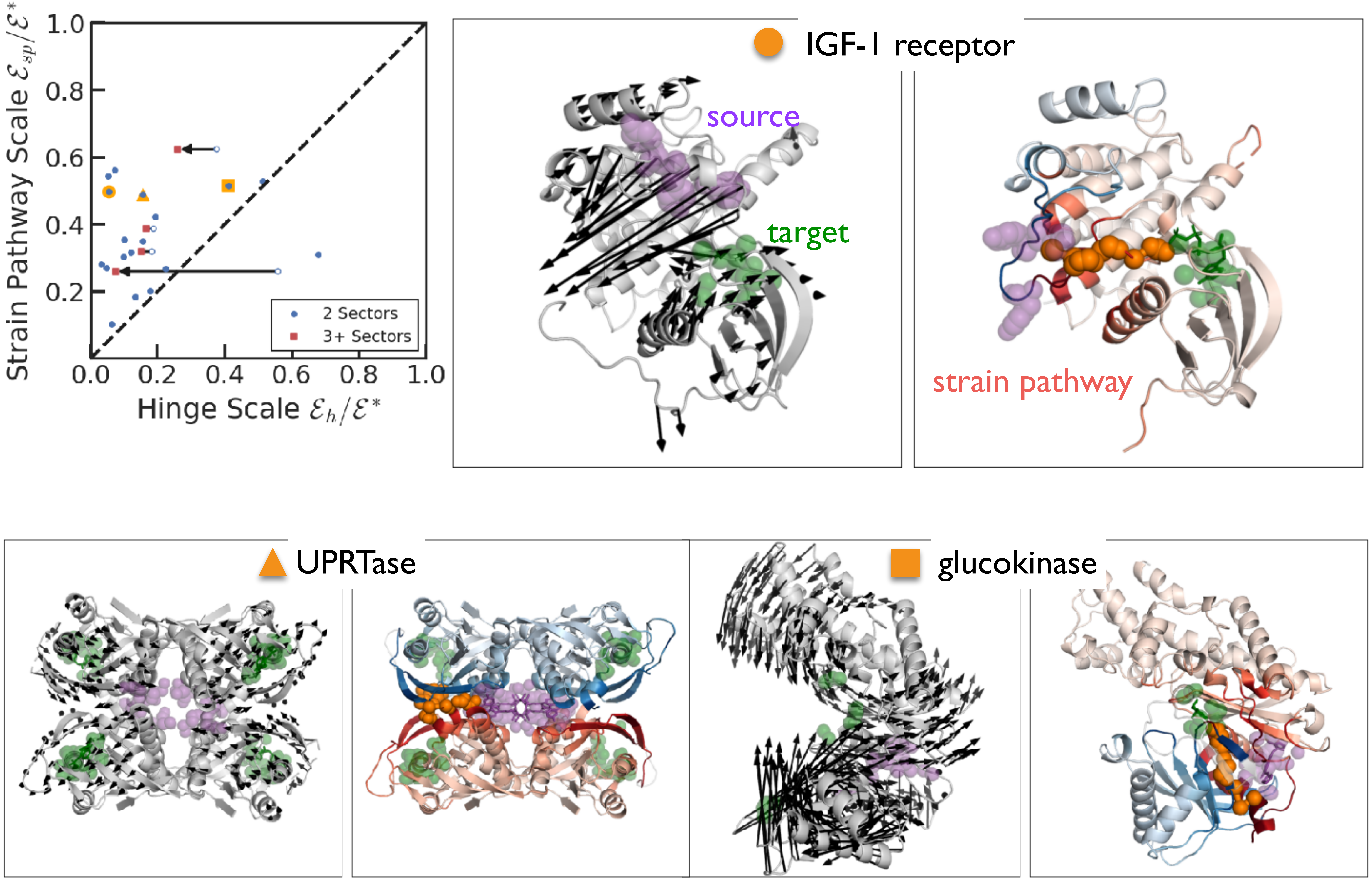
$\delta u_{sp}/\delta u^*$ quantifies significance of strain pathway

Persistent Homology for Mechanical Networks

- Classify with strain pathway scale and hinge scale
- Continuum of mechanisms from hinges to strain pathways
- Perhaps this is why allostery mechanisms have resisted easy classification?!

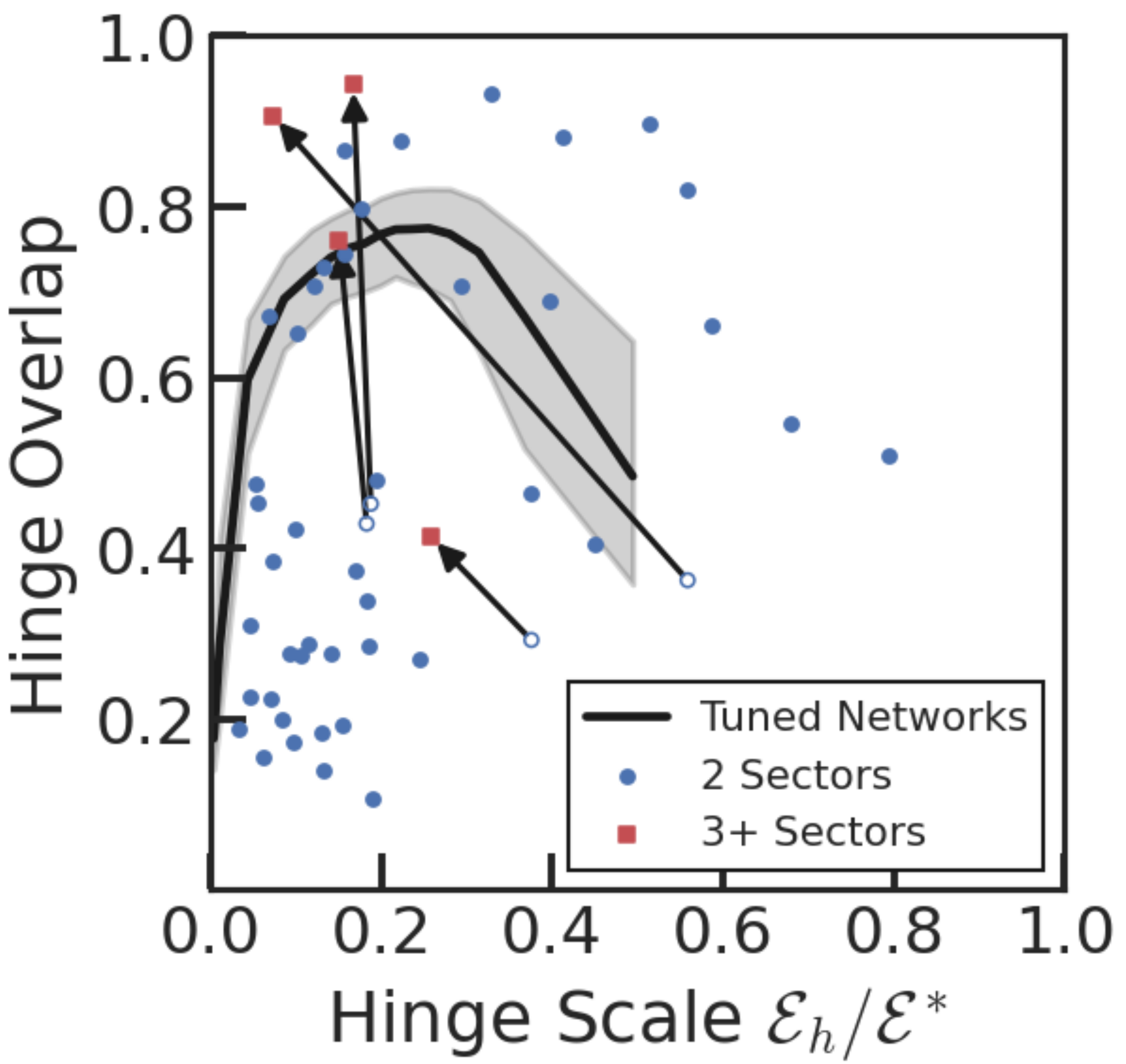


Persistent Homology for Proteins



Persistent Homology Works Reasonably Well for Protein Allostery

- Hinge motion overlap quantifies overlap between predicted and observed
- For sufficiently persistent features, overlap is high
- Drops at very high hinge scale due to fluid/nearly-fluid sectors with large displacements unrelated to allostery



What Did “Statistical Physics” Tell Us?

- We now have designed ensembles
- So what do we want to know??
- How does edge tuning at microscopic scale lead to emergent collective phenomenon of allosteric function at macroscopic scale?
- What happens to networks when they learn allostery?

- Edge tuning affects topological structure of response
- Most topologically significant features (sectors/hinges/strain pathways) are responsible for function

“Statistical Physics” from Big Data

- Summary of our approach:
  - Design ensembles of networks with same function
  - Identify microscopic origin of function with topological data analysis
  - Dimensional reduction: allosteric mechanism reduced to 1(2) variables for electrical/flow (mech) networks
  - Apply analysis to real systems
- What did we learn?
  - Allosteric mechanisms in proteins are not distinct—there is a continuum
  - Mechanism can be specified by two variables that can be extracted from structural measurements

Persistent Homology Works! But Let's Get Even More Ambitious

- We have to apply the inputs in order to carry out PH analysis
- Is it possible to figure out what network has learned without applying inputs? Can we extract the structure-function relation?
- Recall double optimization
  - Cost landscape
    - Cost function: (desired input/output relation - free input/output relation)^2
    - DOF: edge conductances
    - Cost Hessian (2nd derivative of cost function wrt to parameters): need cost function (inputs)
  - Physical landscape
    - power dissipation
    - physical DOF: node pressures/voltages
    - Physical Hessian: doesn't depend on cost function!

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What can we learn from the physical Hessian?

Recall Learning Requires Simultaneous Minimization in Two Landscapes

- Power landscape evolves during learning
  - Power depends on parameters (edge conductances)
- Learning Hessian tells us curvatures in learning phase space

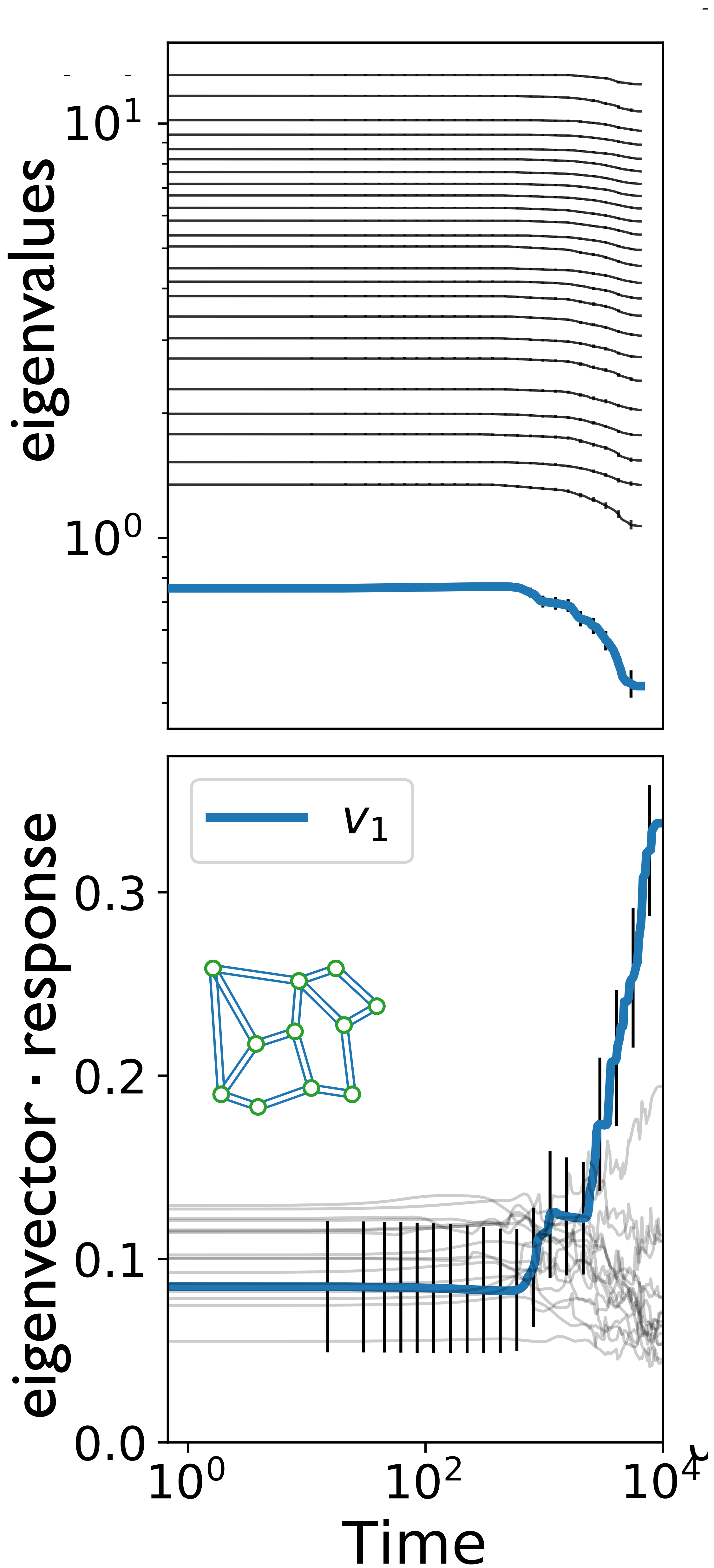
$$H_L = \frac{\partial^2 \mathcal{L}}{\partial k_i \partial k_j}$$

- Eigenvalues of H_L are curvatures, eigenvectors are corresponding directions in learning phase space
- Physical Hessian tells us curvatures in physical phase space

$$H_P = \frac{\partial^2 \mathcal{P}}{\partial V_\alpha \partial V_\beta}$$

GO TO SLIDES

Physical Landscape Flattens in Direction of Learned Response

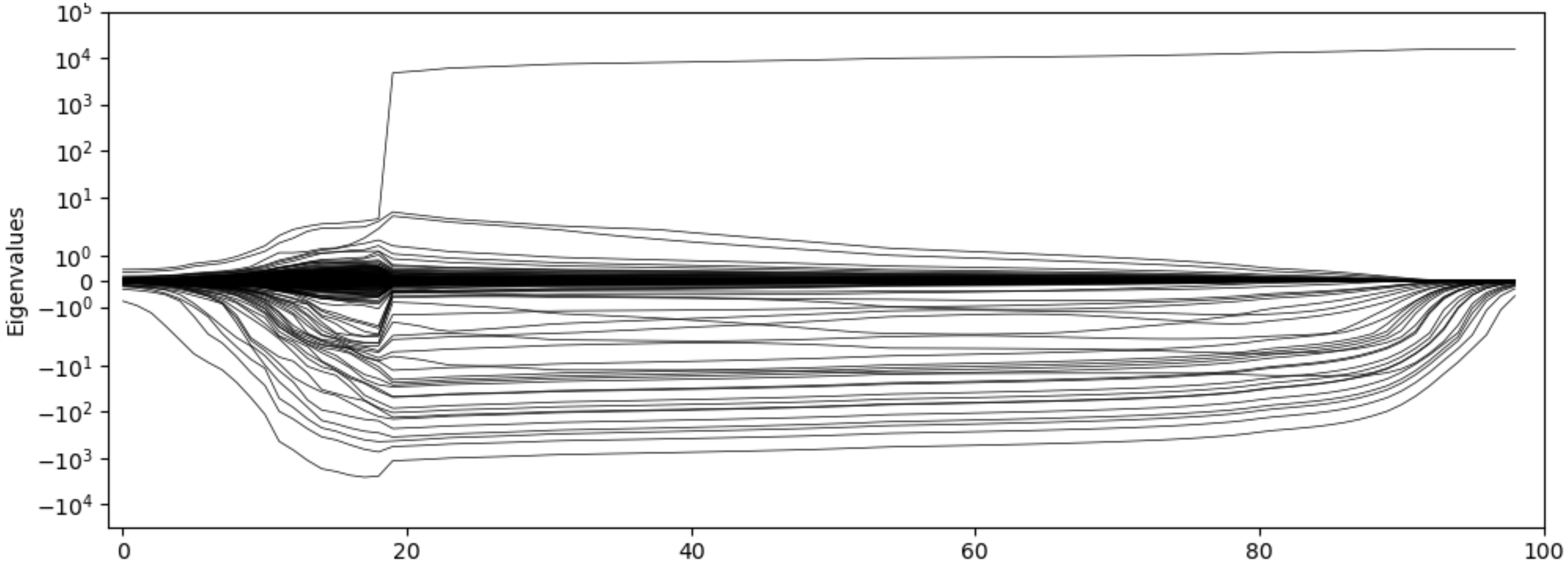


- As system learns

  Stern, Liu, Balasubramanian, PRE (2024)
  - Lowest eigenvalues decrease
  - Lowest eigenvectors overlap more with response to inputs
- Lowest eigenvectors tell us about learned response
- Look at lowest eigenvectors of physical Hessian

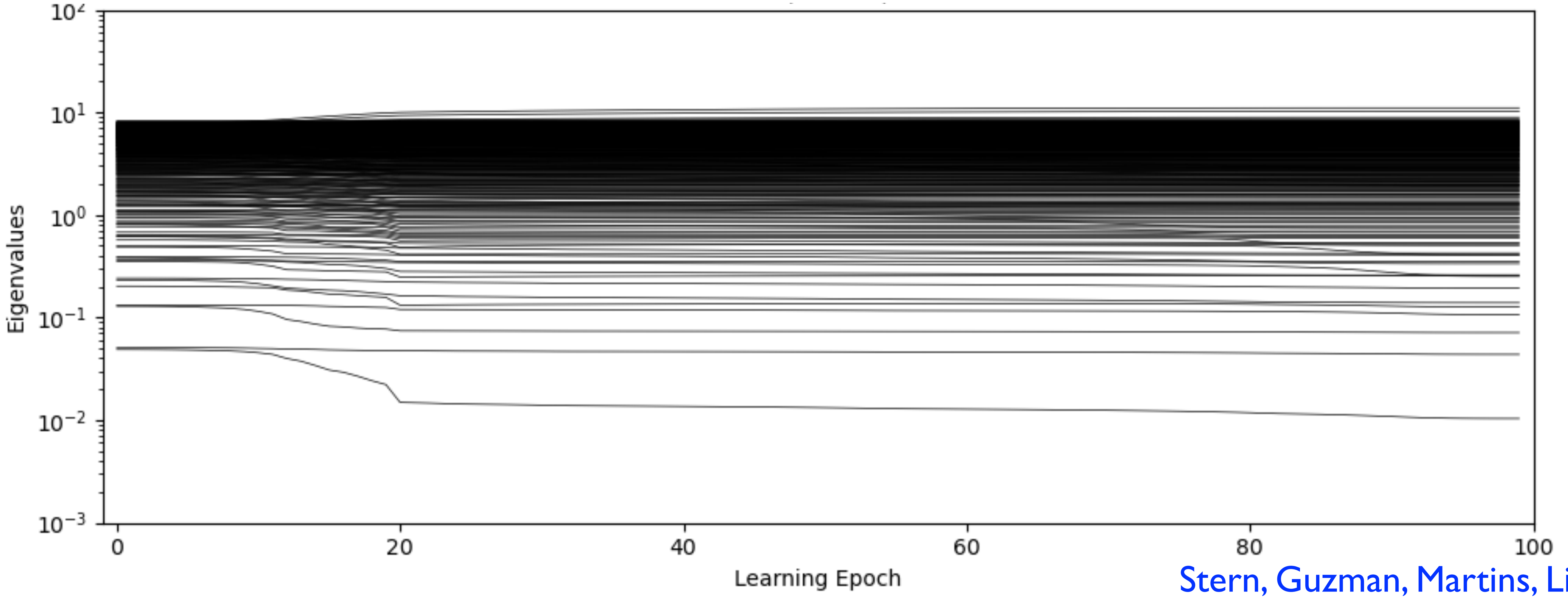
Evolution of Eigenvalues in Learning and Physical Hessians

Learning Hessian H_L



Highest eigenvalues increase

Physical Hessian H_P



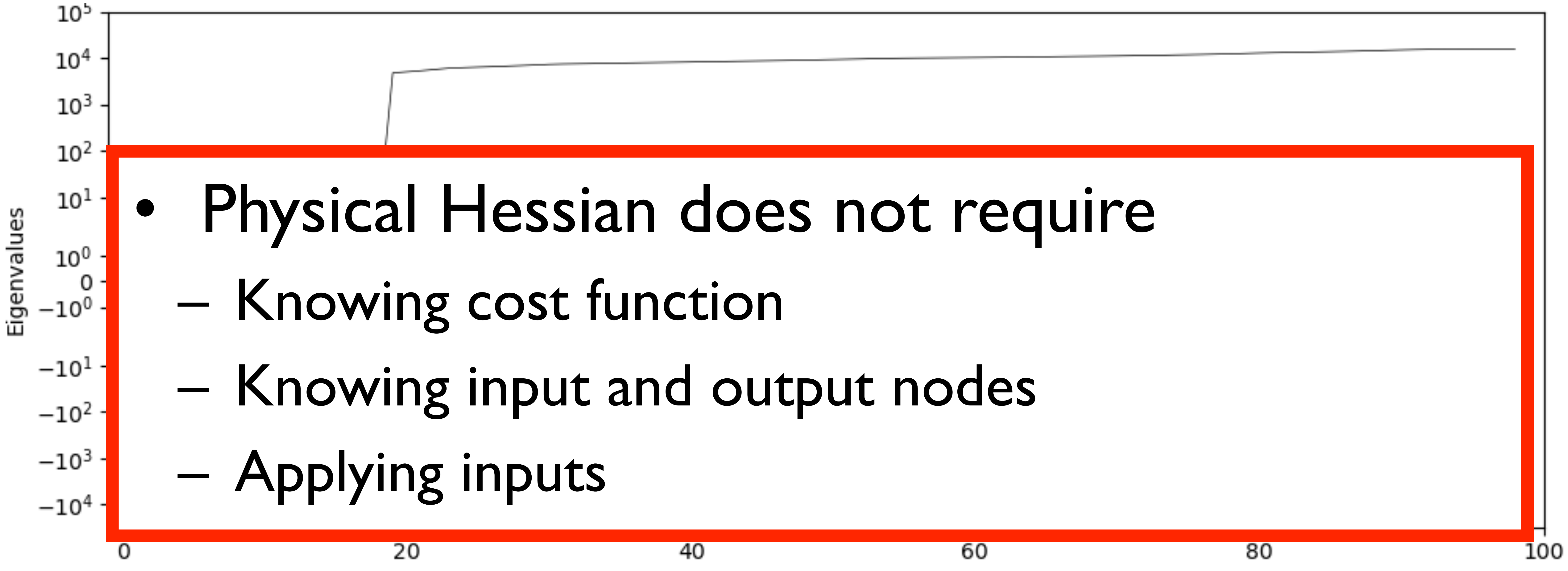
Lowest eigenvalues decrease

$$H_L \sim \left[H_P^{-1}\right]^4$$

Stern, Guzman, Martins, Liu, Balasubramanian arXiv (2024)

Evolution of Eigenvalues in Learning and Physical Hessians

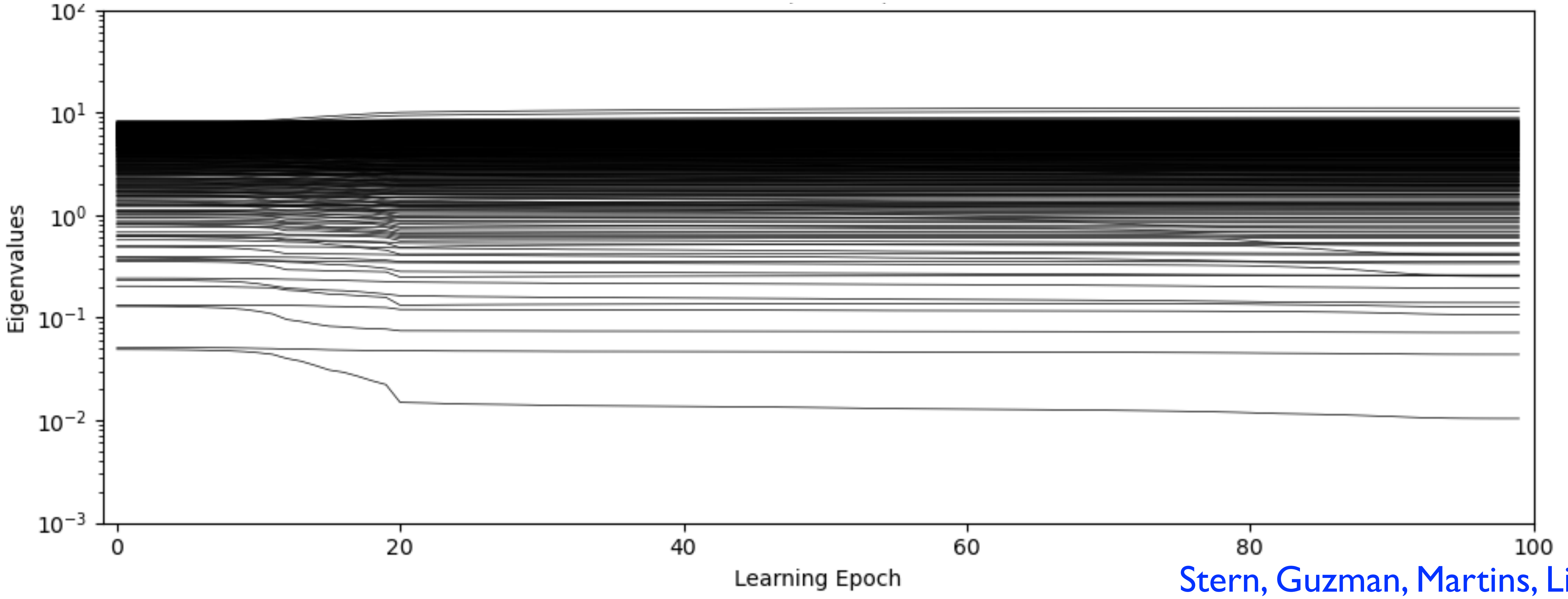
Learning Hessian H_L



- Physical Hessian does not require
  - Knowing cost function
  - Knowing input and output nodes
  - Applying inputs

Highest eigenvalues increase

Physical Hessian H_P



Lowest eigenvalues decrease

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Stern, Guzman, Martins, Liu, Balasubramanian arXiv (2024)

Lowest Mode of Physical Hessian Corresponds to Highest Mode of Cost Hessian

from physical Hessian | from learning Hessian | overlap

1 source edge: $\Delta V = 1V$

1 target edge: $\Delta V = 1V$

Felipe Martins, Marcelo Guzman