Shaping life via a series of cellular redox bombs

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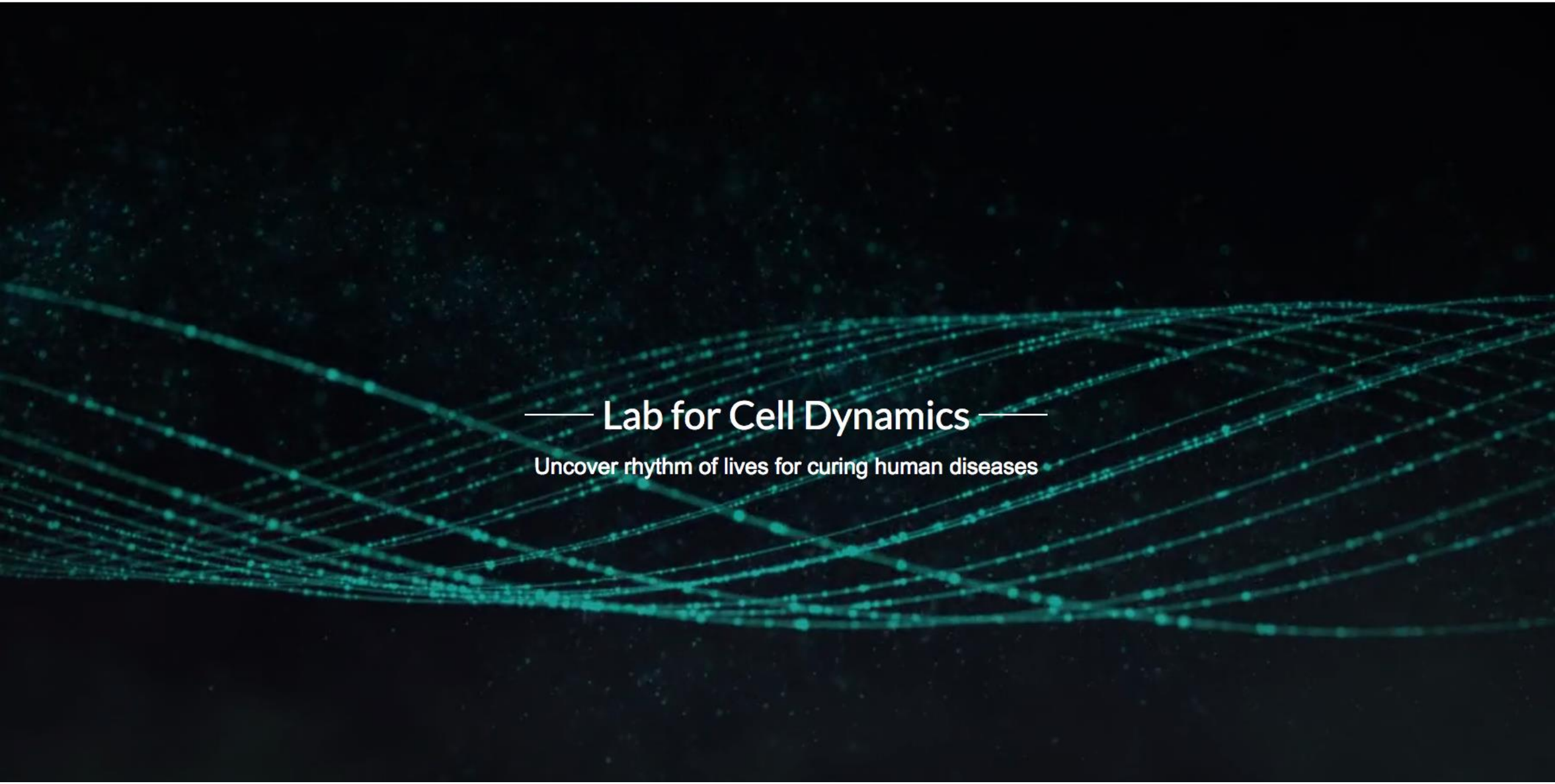
通俗演講 Colloquium
May/13/2025

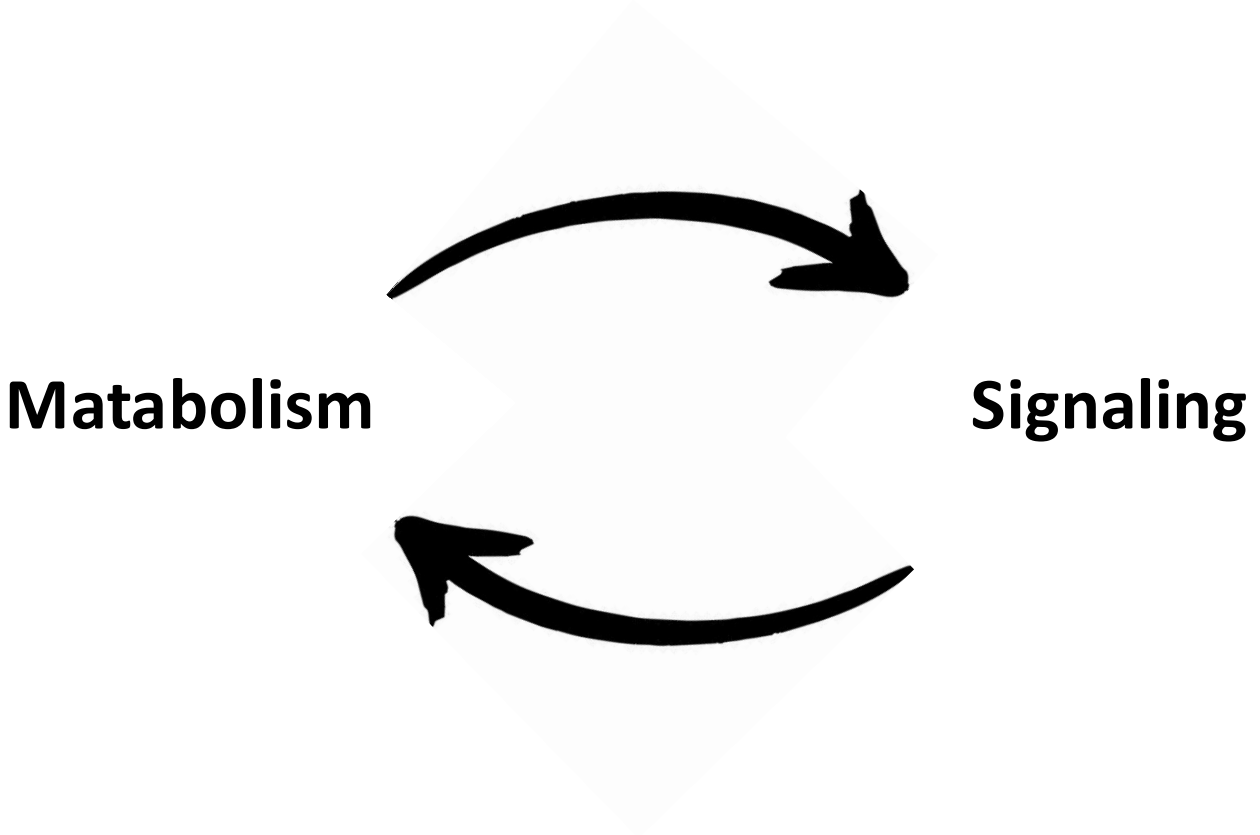

Lab for Cell Dynamics
Uncover rhythm of lives for curing human diseases

Dynamics are important!

Dynamics are important!

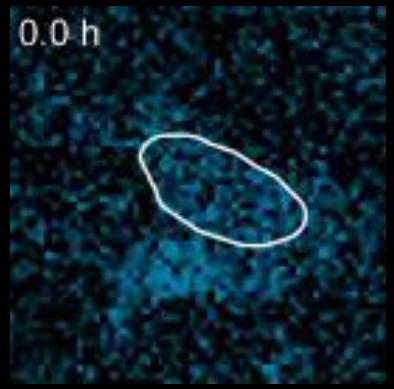
time

Dynamics of metabolism-signaling



Biological dynamics across time and space

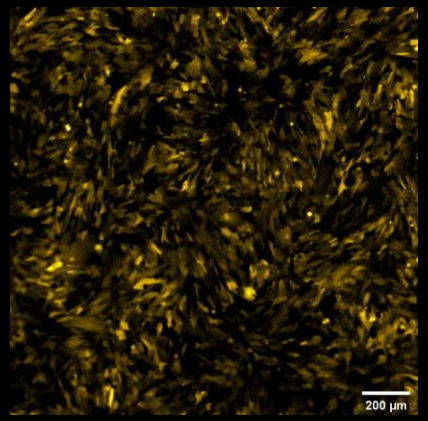
in time



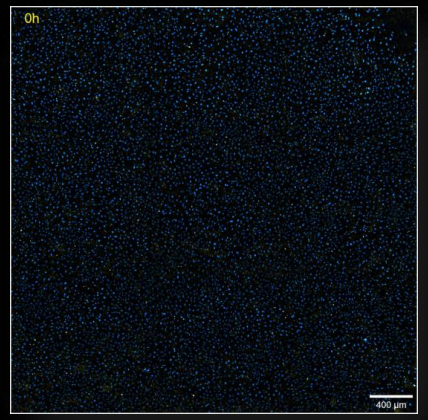
Oscillations

Bistable switch

in space



Self-organization



Trigger waves

Acknowledgements

Hannah Katrina Co
TIGP MCB program

Chia-Chou Wu

Acknowledgements

Hannah Katrina Co
TIGP MCB

Chia-Chou Wu

The Thinker

Auguste Rodin (1904)

Nature is a fascinating sculptor

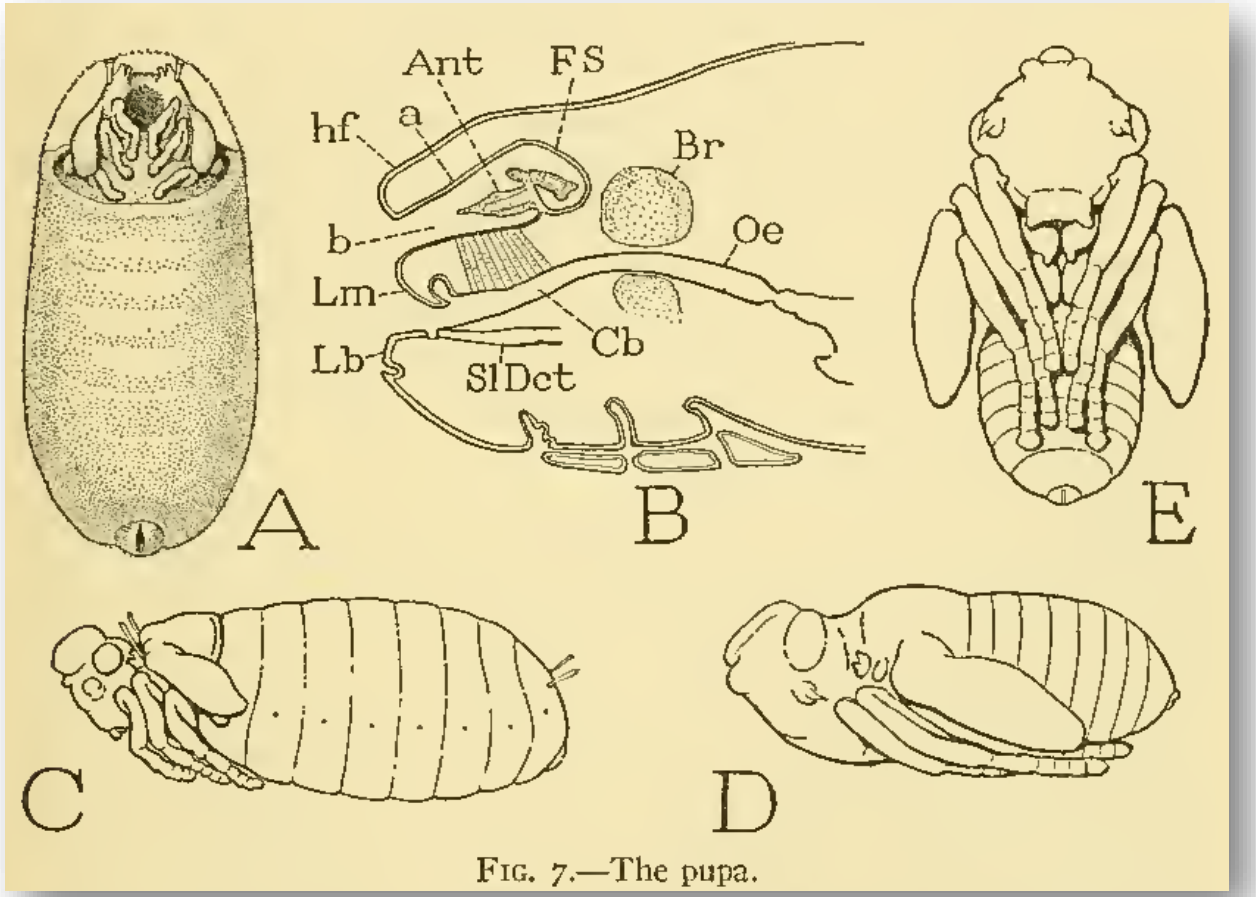
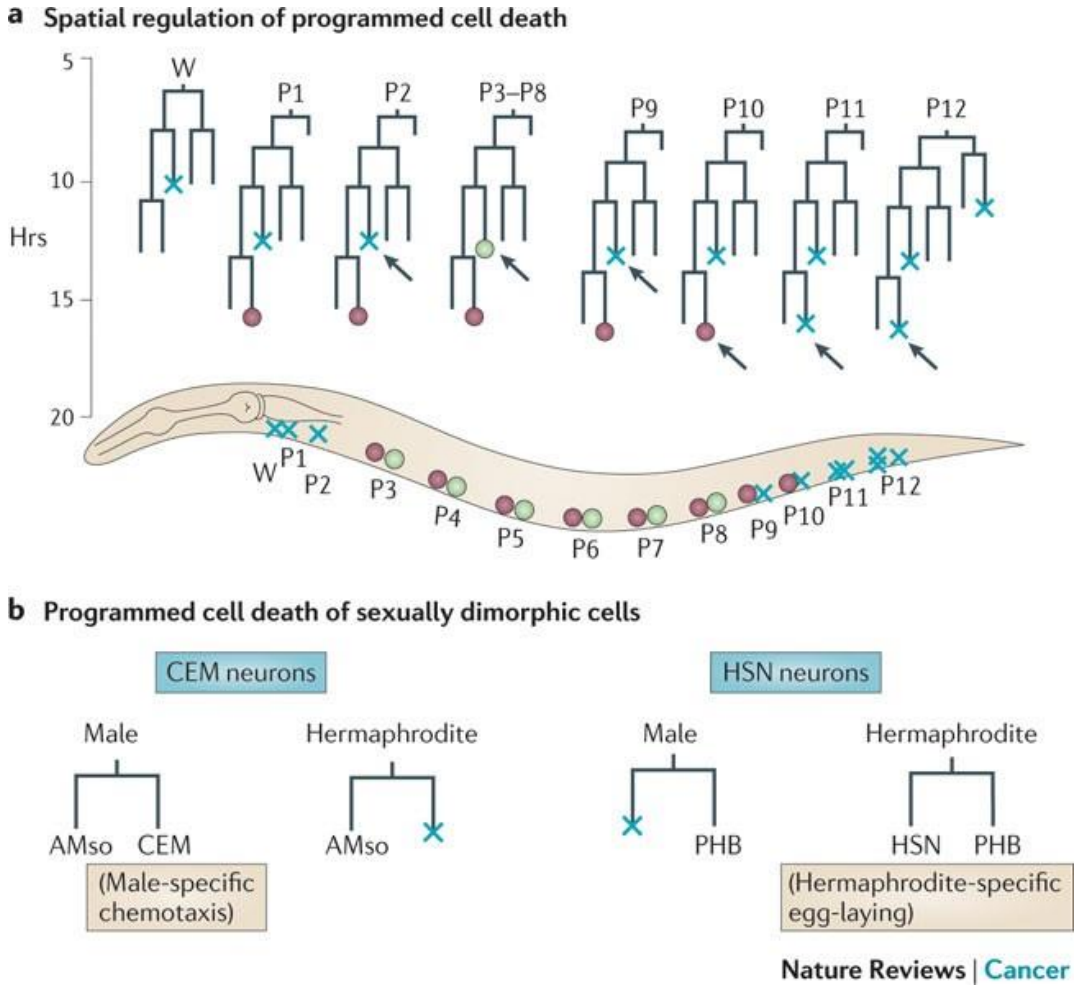


Fig. 7.—The pupa.

Weismann A (1864a)

Cell death during embryogenesis—
Identify programmed cell death, apoptosis, in *C. elegans*



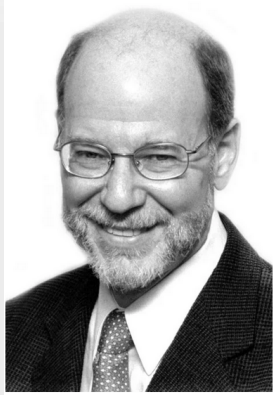


Photo from the Nobel Foundation archive.

H. Robert Horvitz
The Nobel Prize in Physiology or Medicine 2002

Born: 8 May 1947, Chicago, IL, USA

Affiliation at the time of the award: Massachusetts Institute of Technology (MIT), Cambridge, MA, USA

Prize motivation: "for their discoveries concerning genetic regulation of organ development and programmed cell death'"

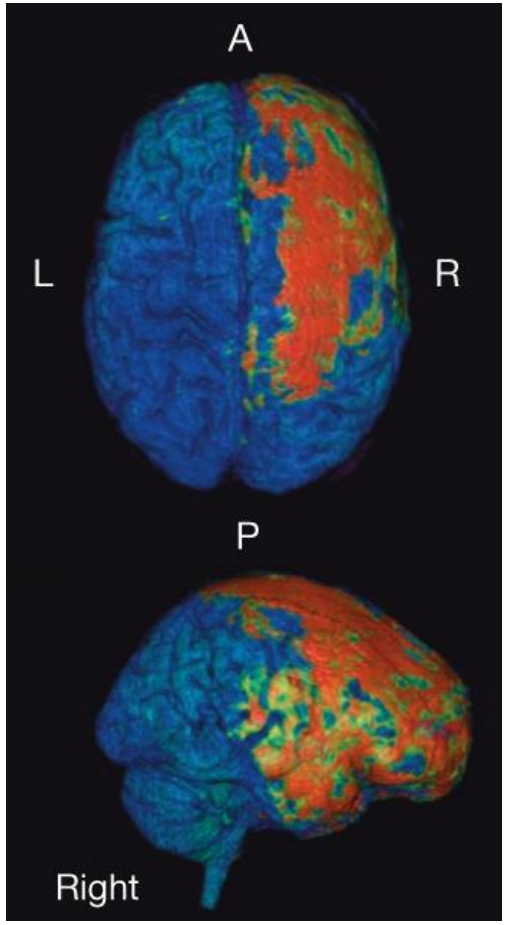
Large-scale cell death during embryogenesis of complex organisms

Death in Embryonic Systems

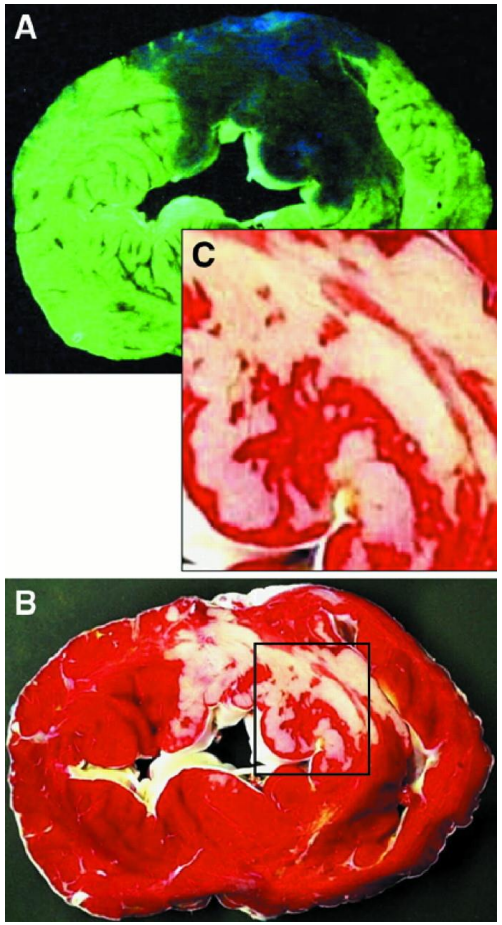
" Abundant death, often cataclysmic in its onslaught, is part of early development in many animals; it is the usual method of eliminating organs and tissues that is useful only during embryonic or larval life"

- John W. Saunders, Jr. (Science, 1966)

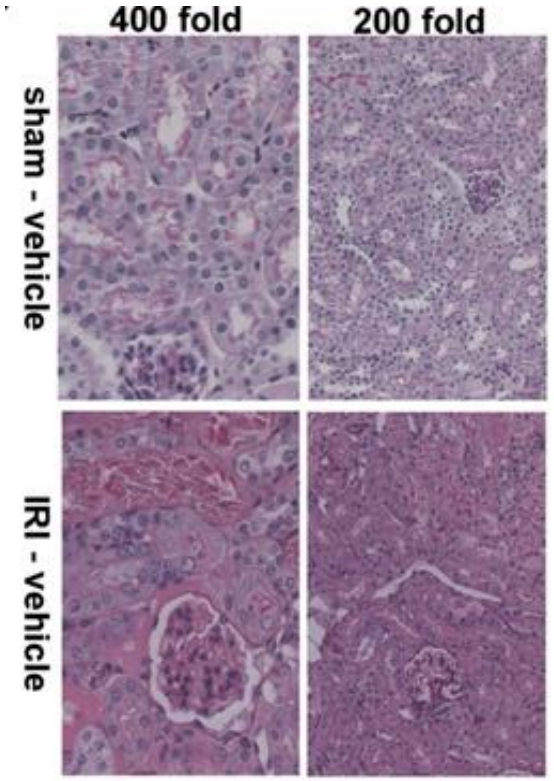
Large-scale cell death occurs in disease pathologies



Roth, T., Nayak, D., Atanasijevic, T. *et al.* (2014) Nature.



Garcia-Dorado, D., Ruiz-Meana M (2000) News Physiol. Sci.

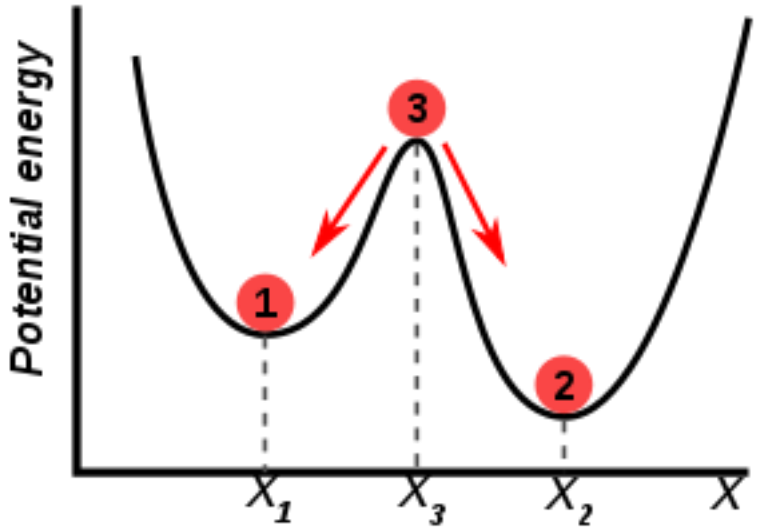


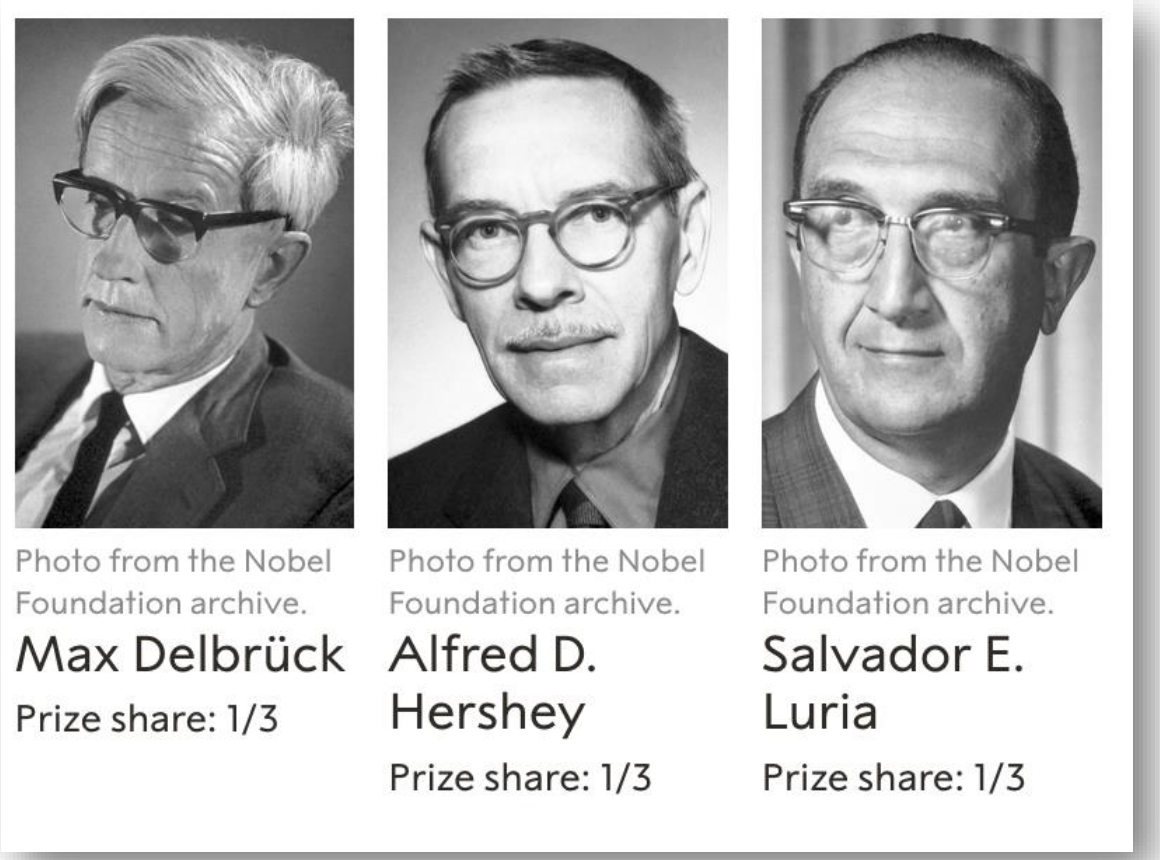
Linkermann, A. *et al.* (2014) PNAS

A century-old question:
how does large-scale cell death occur?

First proposal of bistable systems

Enzyme systems with alternative steady states. In Unités Biologiques Douées de Continuité Genetique (International Symposium CNRS No. 8). (Paris: Editions du CNRS), pp. 33–34. Delbrück, M. (1949).





Nobel Prize in Physiology or Medicine 1969

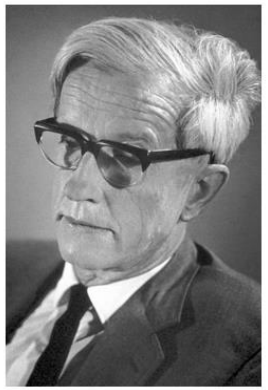
Formulate mathematical models for bistability of lac operon activity

Bi-stability

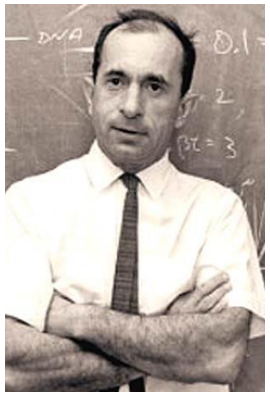
- Memory of lac operon
- Switch in states
- System dynamics
- Boolean logic
- Nonlinear feedback
- Bring exp and theory together

Max Delbrück (1949)

Enzyme systems with alternative steady states. In Unités Biologiques Douées de Continuité Genetique (International Symposium CNRS No. 8). (Paris: Editions du CNRS), pp. 33–34.

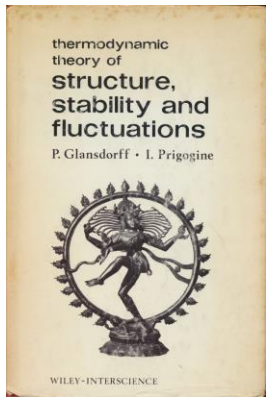


Arron Novick(1957)



Glansdorff, P. Prigogine, I.,(1971)

Thermodynamics of Structure,
Stability and Fluctuations.Wiley, New York



Babloyantz, A. and Sanglier, M (1972)

Chemical instabilities of "all-or none" type in β-galactosidase induction and active transport. FEBS Lett. 1972, 23: 364-366.

Thomas, R., (1973)

Boolean formalisation of genetic control circuits. J. Theoret. Biol. 1973, 42: 563-585.

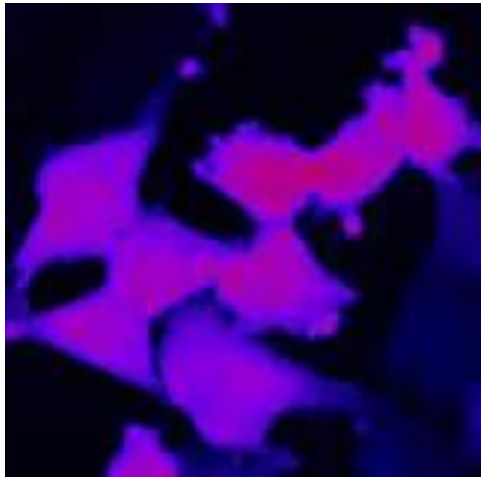
Nicolis, G. and Prigogine, I., (1977)

Self-Organization in Nonequilibrium
Systems. From Dissipative Structures to Order through
Fluctuations. John Wiley and Sons, New York, 1977, pp. 387-394

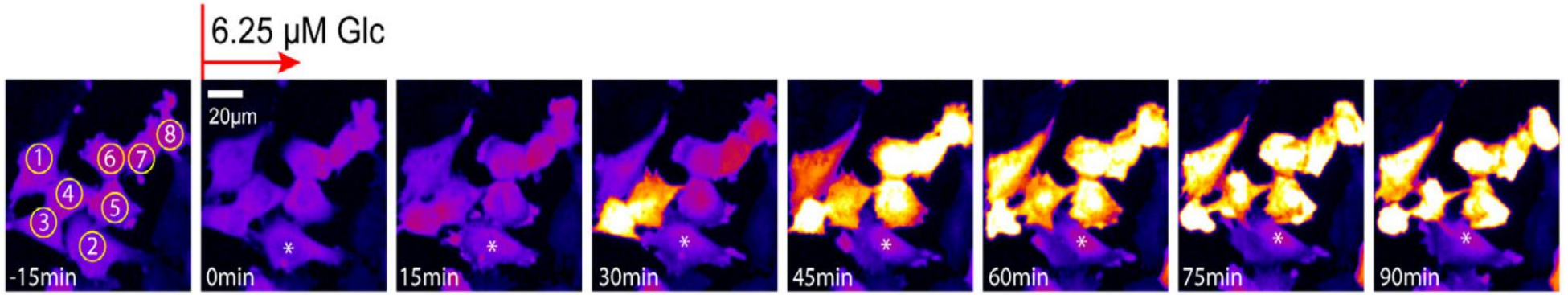
Ozbudak, E.M., Van Oudenaarden, A. *etc*, (2004)

Multistability in the lactose utilization network of Escherichia coli. Nature 2004, 427: 737-740.

Switch-like elevation of ROS upon glucose starvation

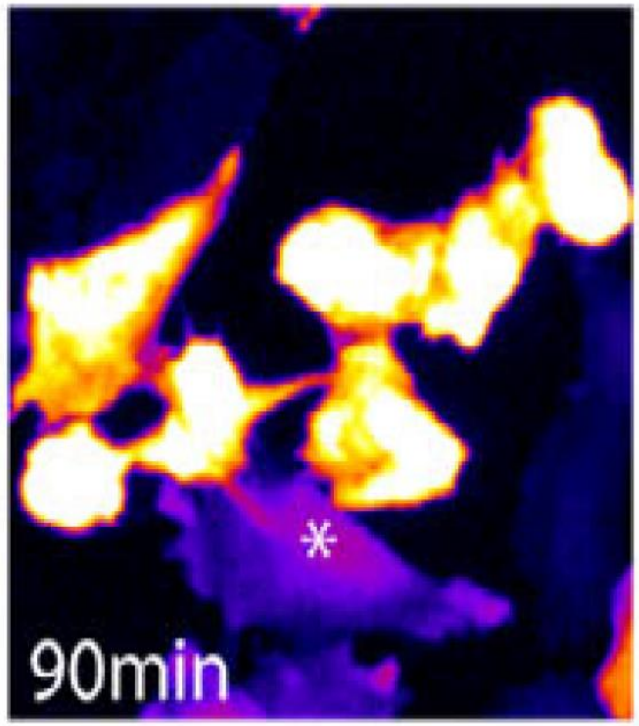


Jo-Hsi Huang Hannah K. C. Co



Molecular Systems Biology **17**: e10480 | 2021

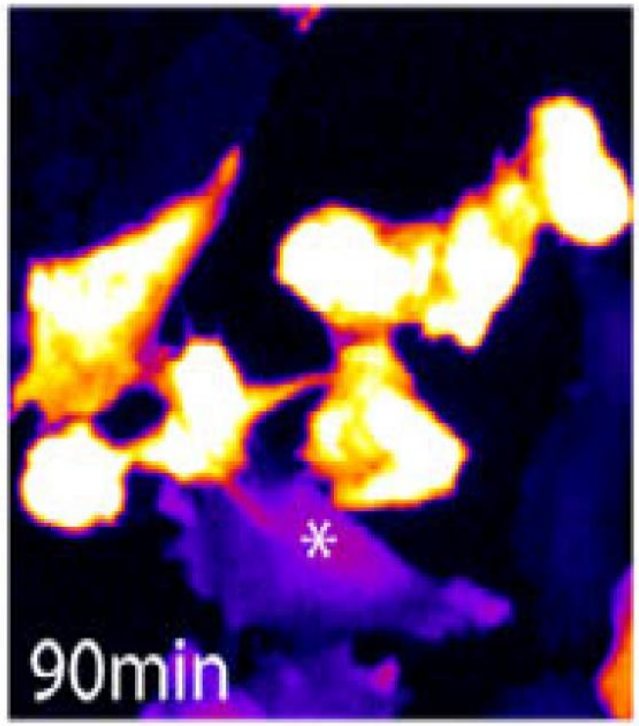
Redox bistable switches can act like biochemical bombs



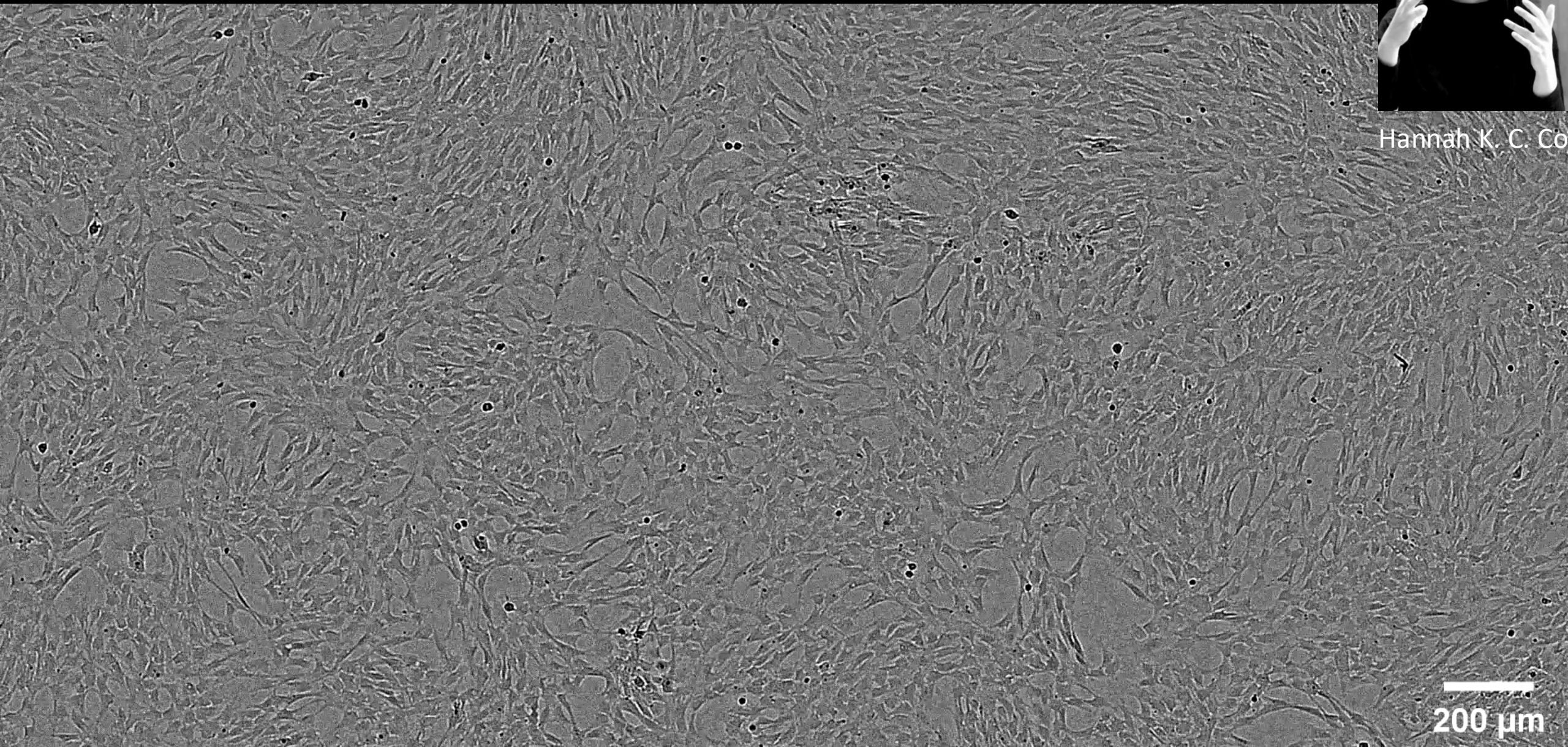
Chemical bombs can be powerful, especially when they are **physically coupled**

Chemical bombs can be powerful, especially when they are **physically coupled**

Redox bistable switches can act like biochemical bombs



Cystine starvation leads to cell death propagation



Hannah K. C. Co

Cystine starvation leads to cell death propagation

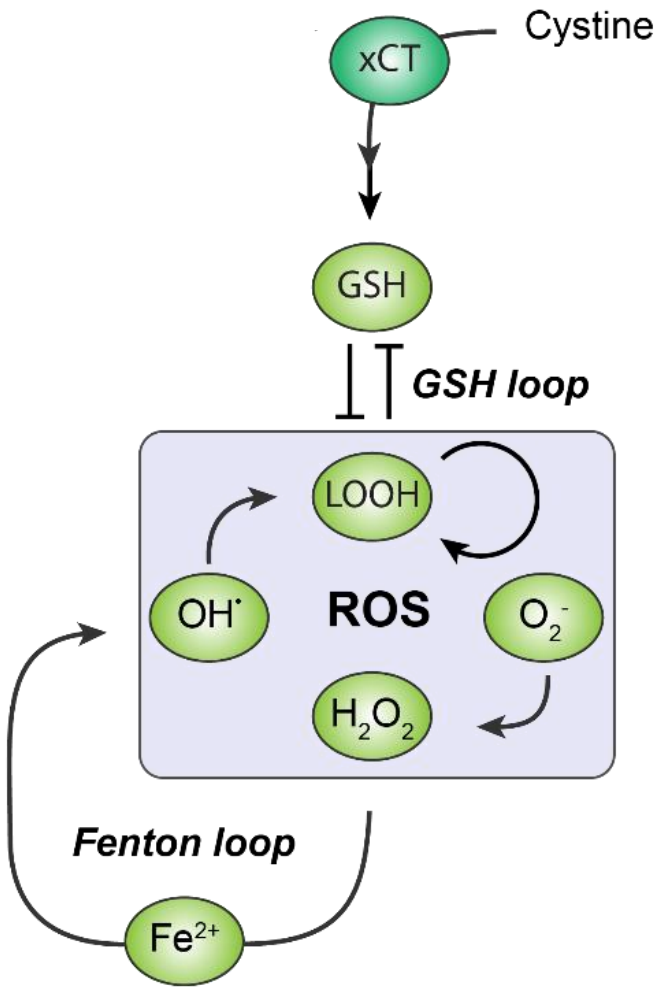
Emergence of large-scale cell death via trigger waves of ferroptosis

Supplementary Video 1a. Ferroptosis spreads across cells in 15 cell lines: RPE-1, 786-O, HuH-7, A-172, Hs 895.T, HeLa, SH-SY5Y, G-402, HOS, LN-18, U-118 MG, PANC-1, MDA-MB-231, H1650, HT-1080

Hypothesis:

large-scale cell death occurs via **ferroptotic trigger waves**

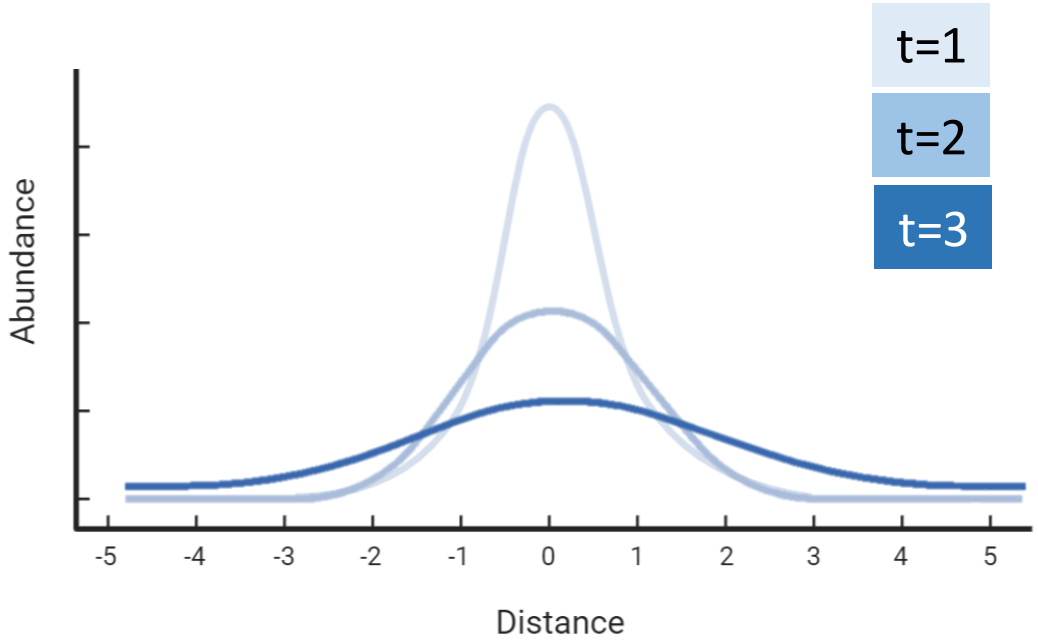
Ferroptosis is an ROS & iron-mediated cell death



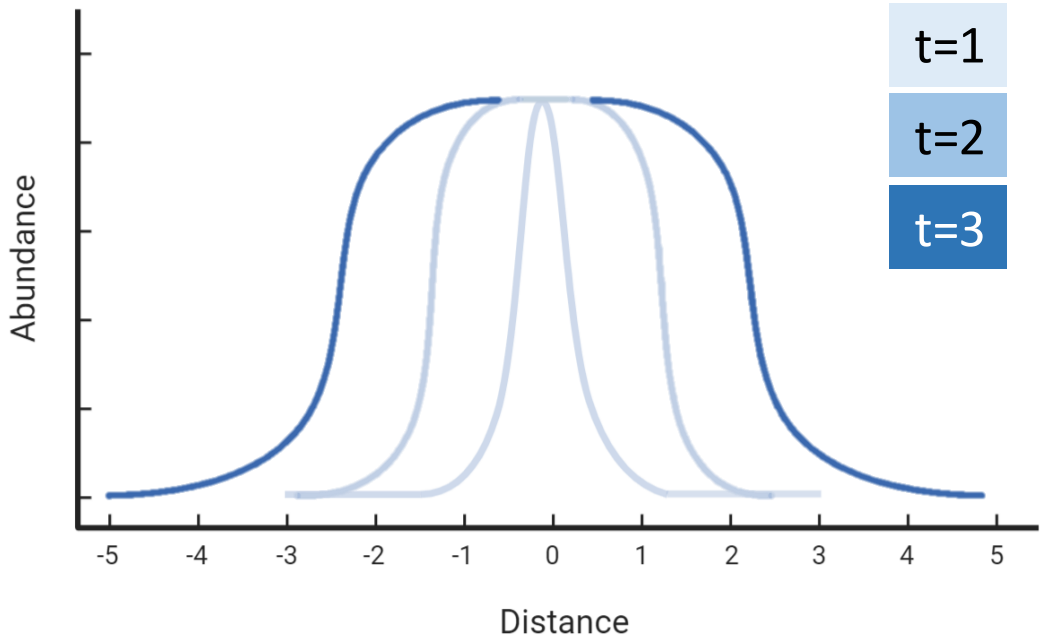
Cell Reports Physical Science 4, 101683, December 20, 2023

Trigger waves maintain signal intensity and transmission speed

Diffusion



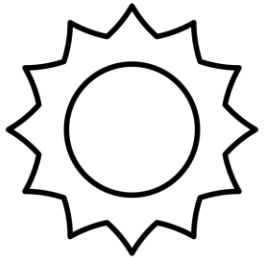
Trigger wave



Wild fires are an example of trigger waves

Components of a trigger wave

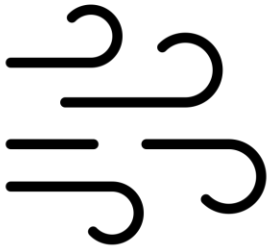
1. Initiation point



Heat/Ignition

2. Spatial coupling mechanism

- Diffusion
- Cell-cell communication



Air

3. Feedback loop

Fuel

Components of a trigger wave

1. Initiation point

Heat/Ignition

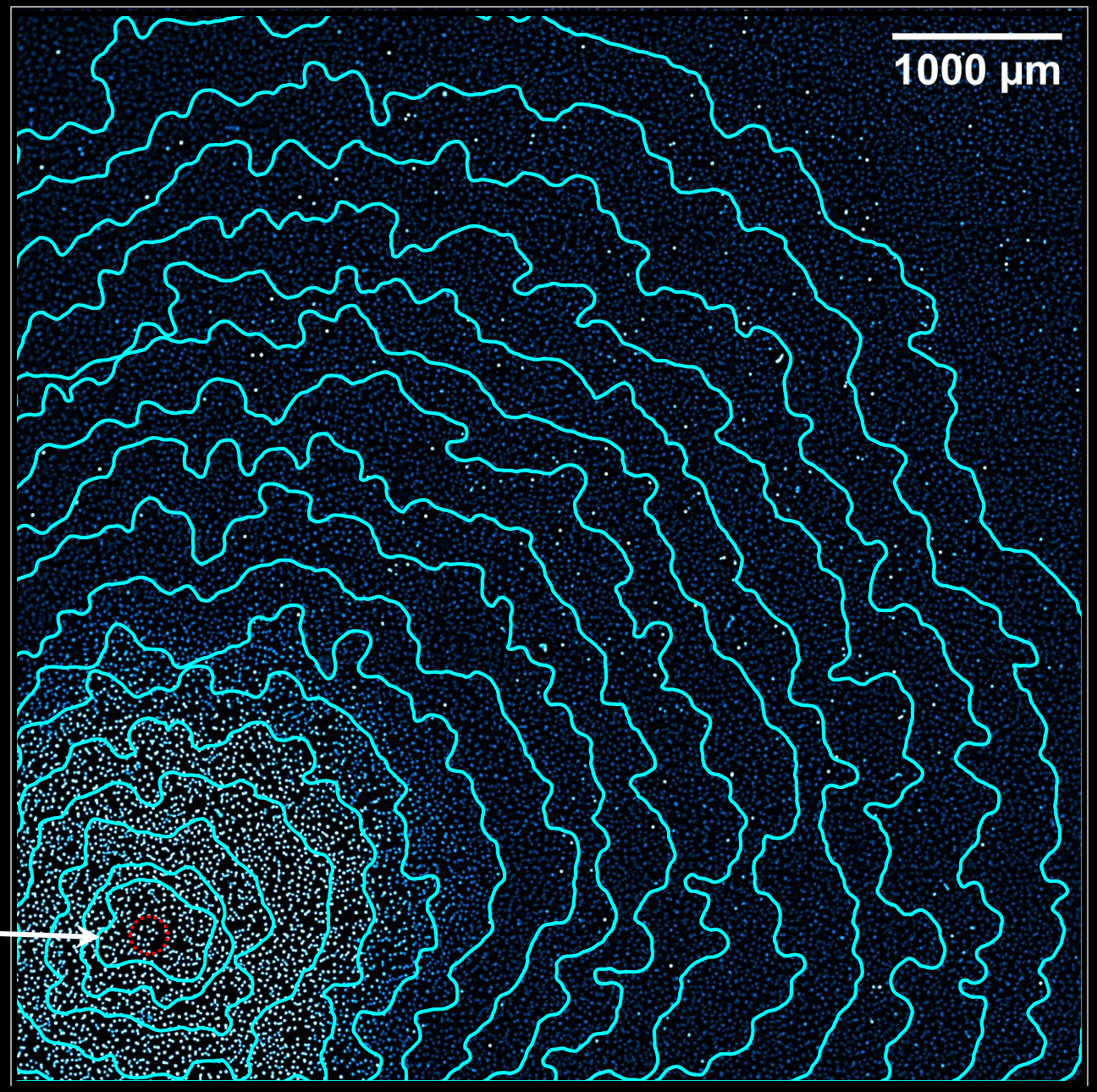
3. Positive feedback loop

Fuel

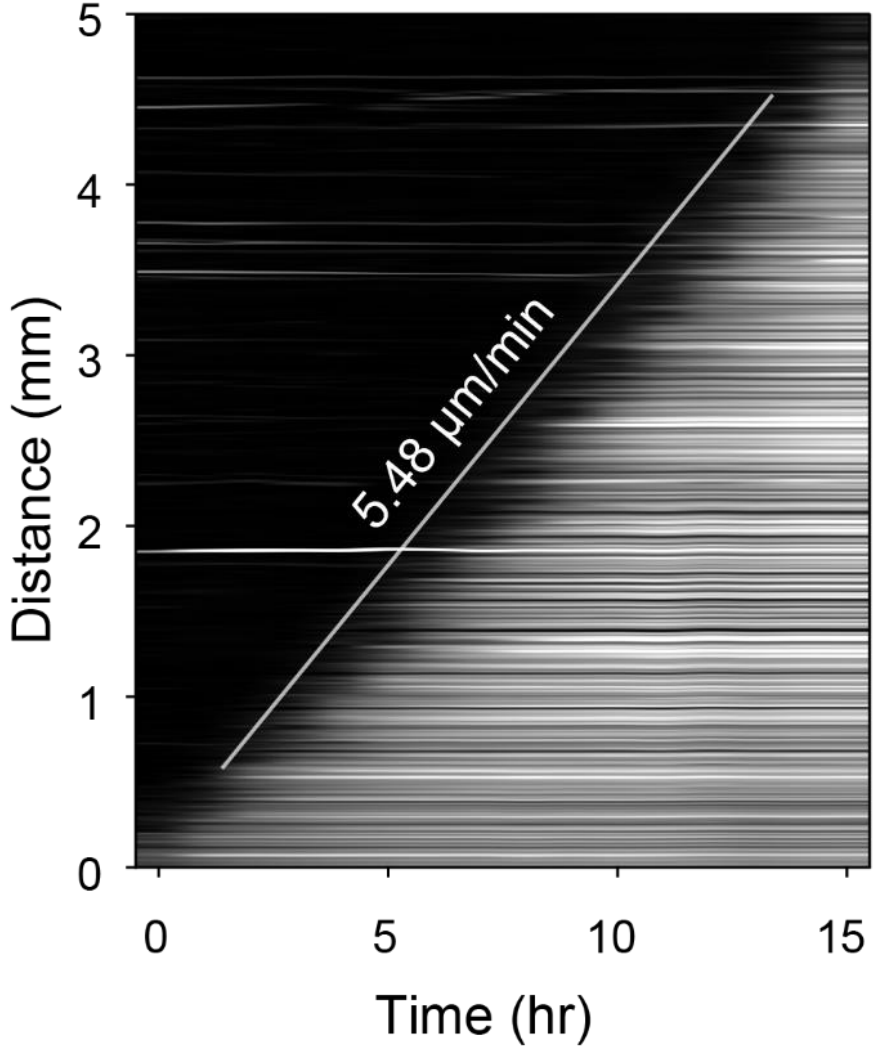
2. Spatial coupling mechanism
- Diffusion
- Cell-cell communication

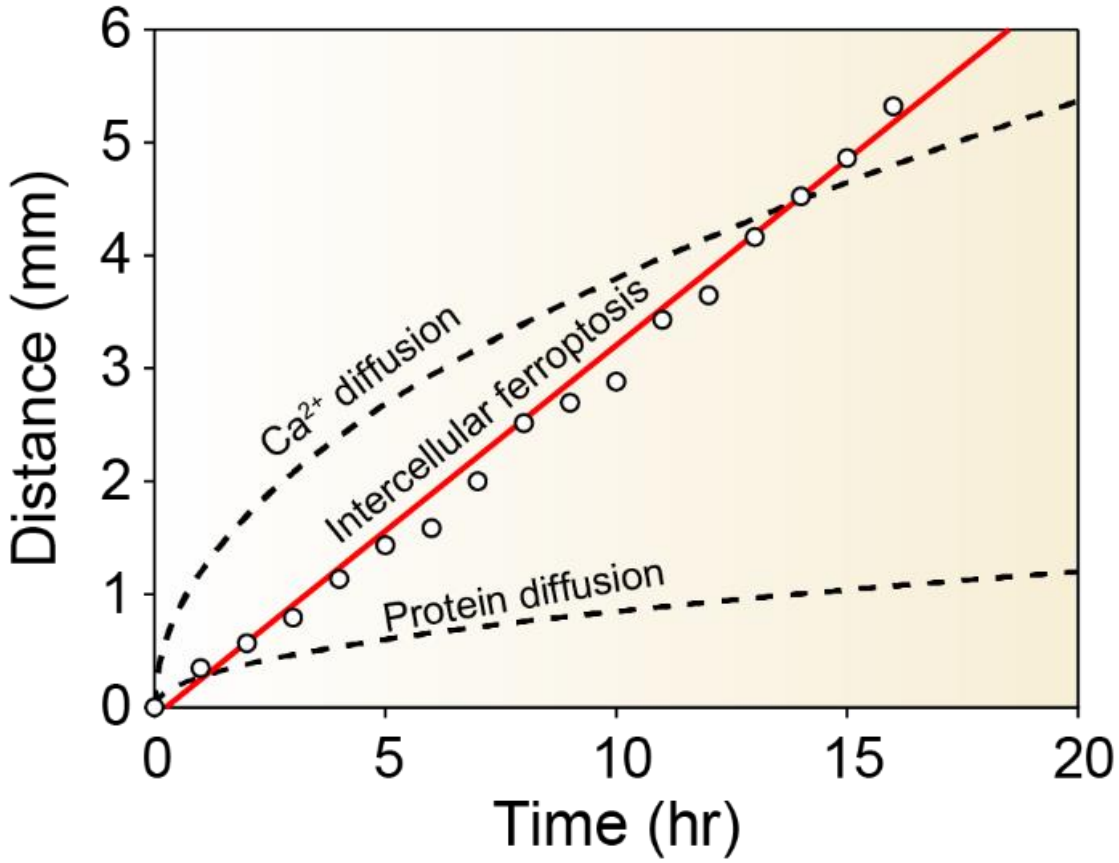
Air

Ferroptosis propagates at a constant speed over long distances

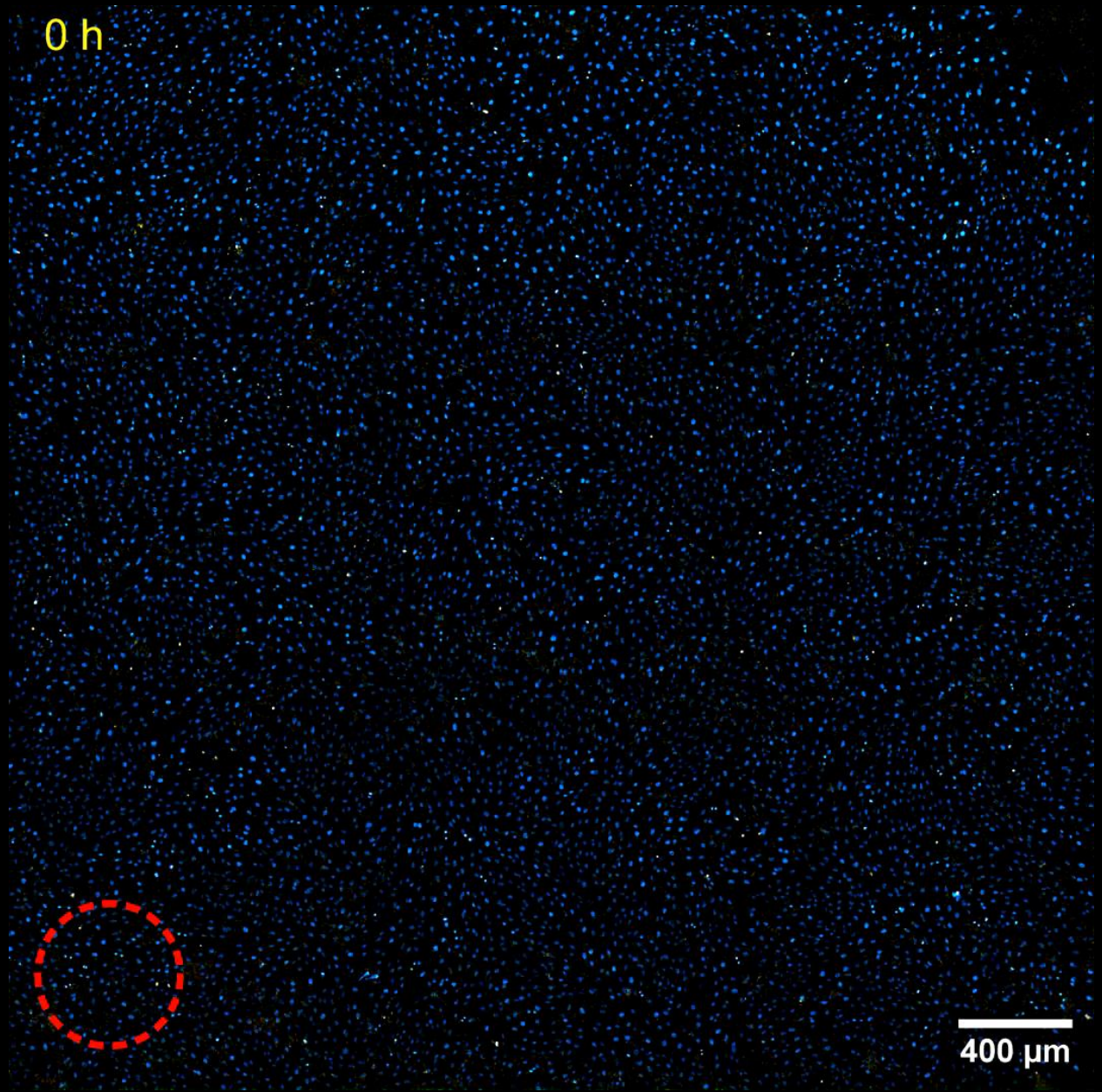


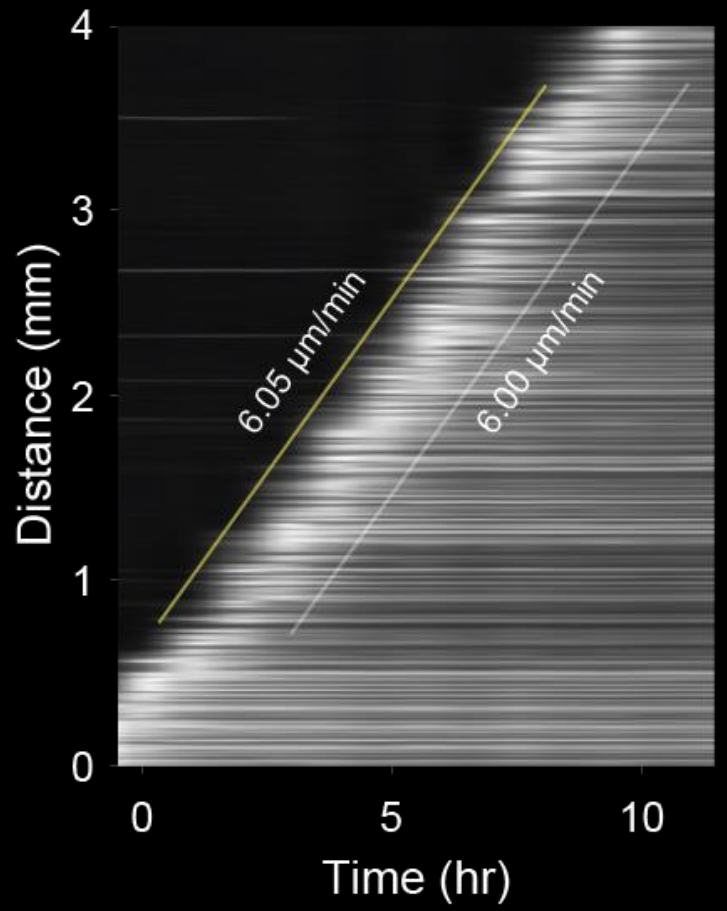
Ferroptosis propagates with a constant speed





Ferroptosis propagates with lipid ROS wave fronts





Components of a trigger wave

1. Initiation point

Heat/Ignition

2. Spatial coupling mechanism

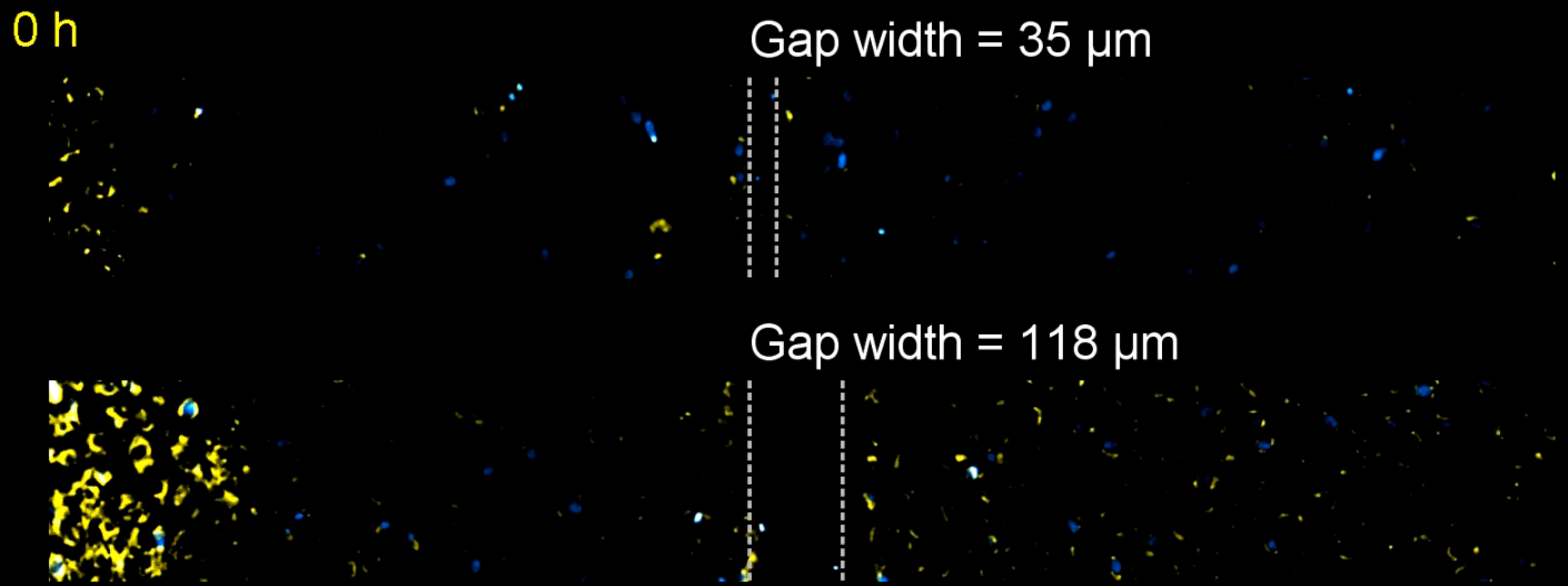
- Diffusion
- Cell-cell communication

Air

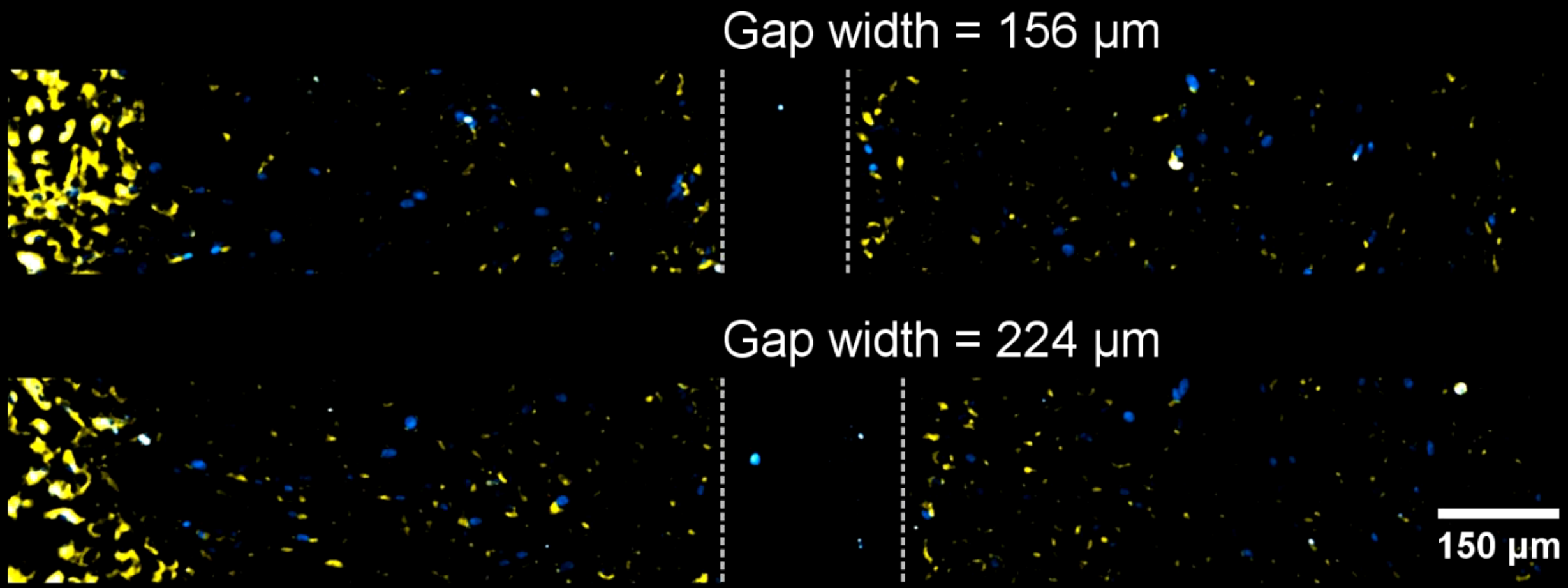
3. Positive feedback loop

Fuel

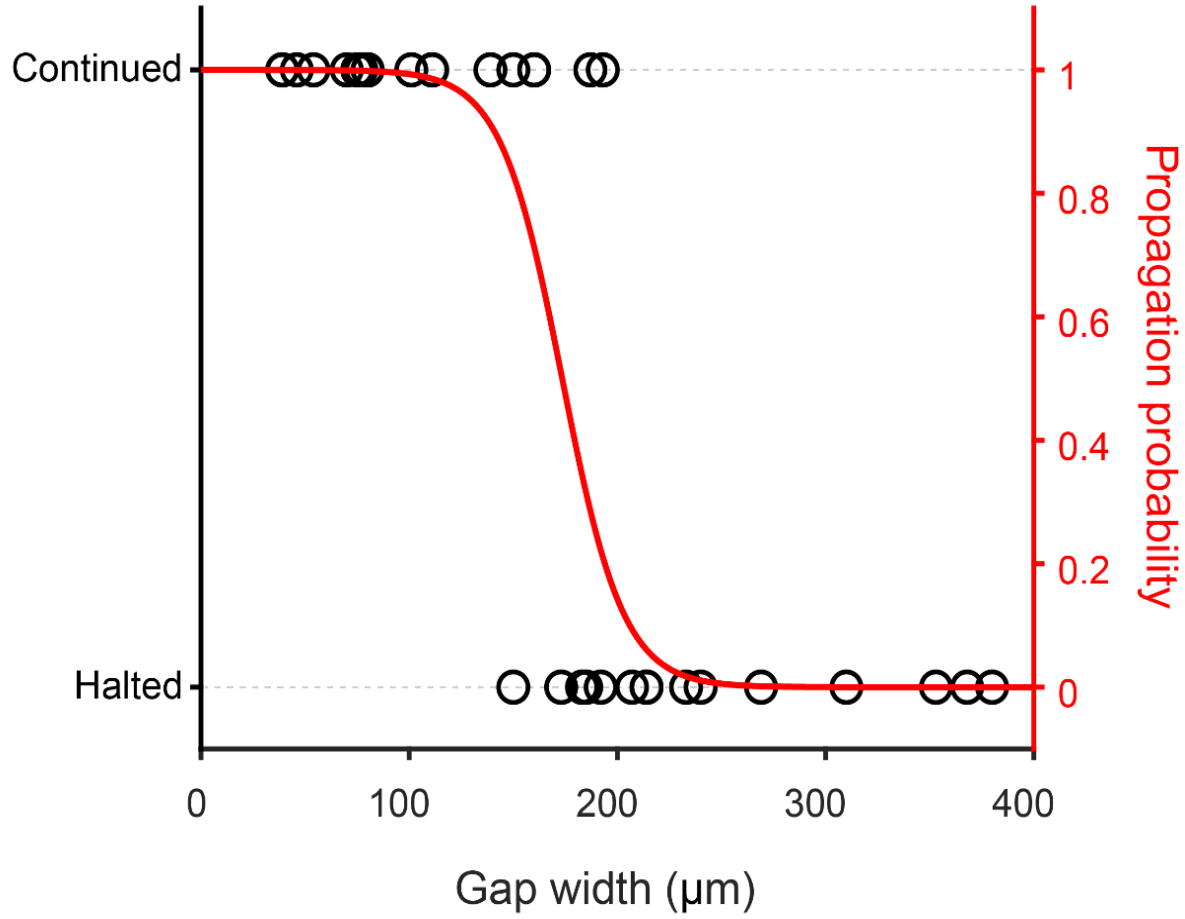
Ferroptosis propagates across gaps < ~ 150 µm



Ferroptosis can be halted by gaps > ~ 150 µm



ROS propagates across physical gaps of ~ 150 µm



Components of a trigger wave

1. Initiation point

Heat/Ignition

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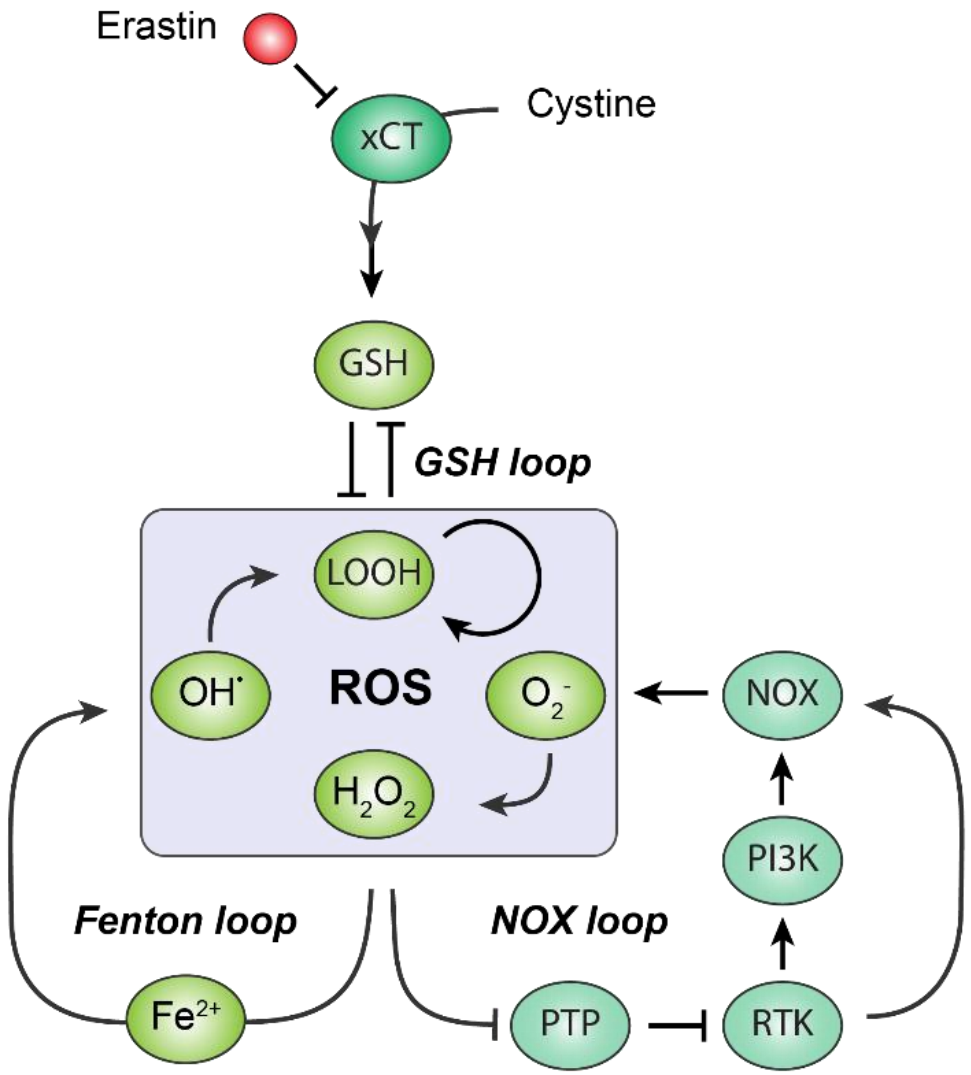
Air

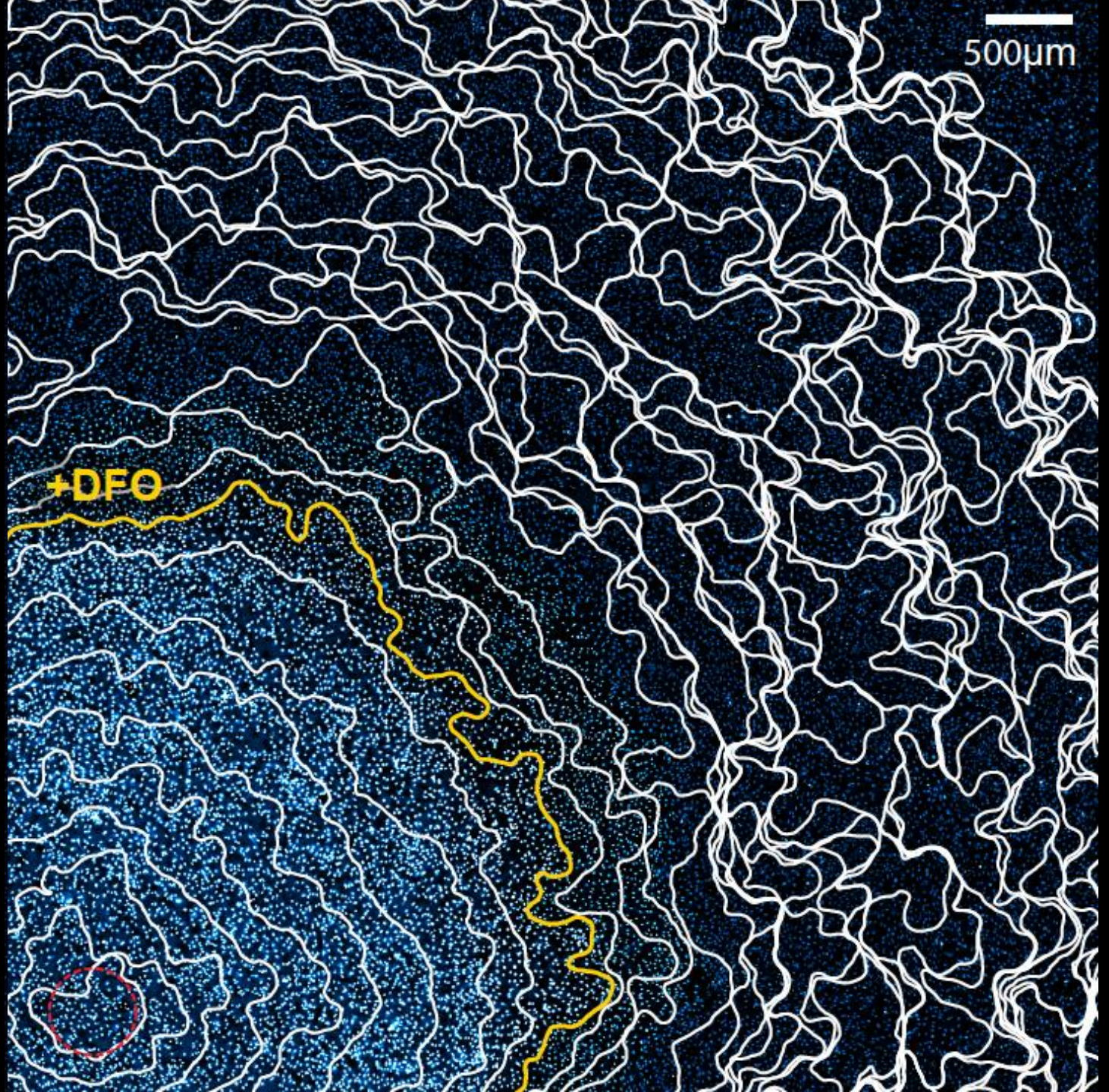
3. Feedback loop

Fuel

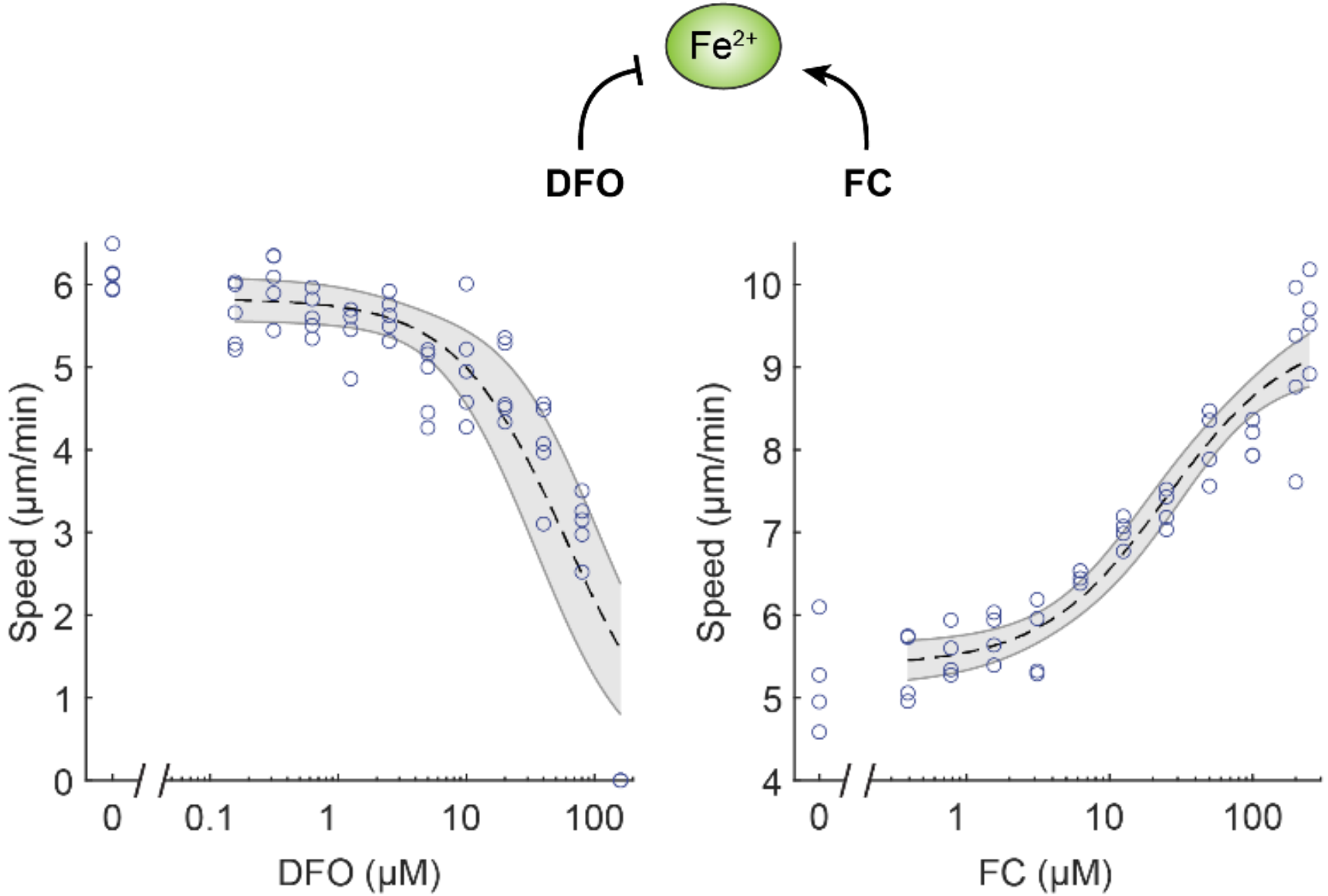
Multiple feedback loops in the ferroptosis regulatory network



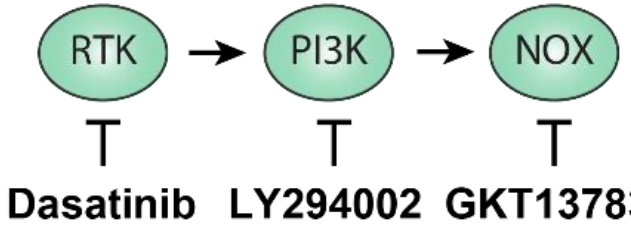
Iron chelation slows down ferroptotic trigger waves

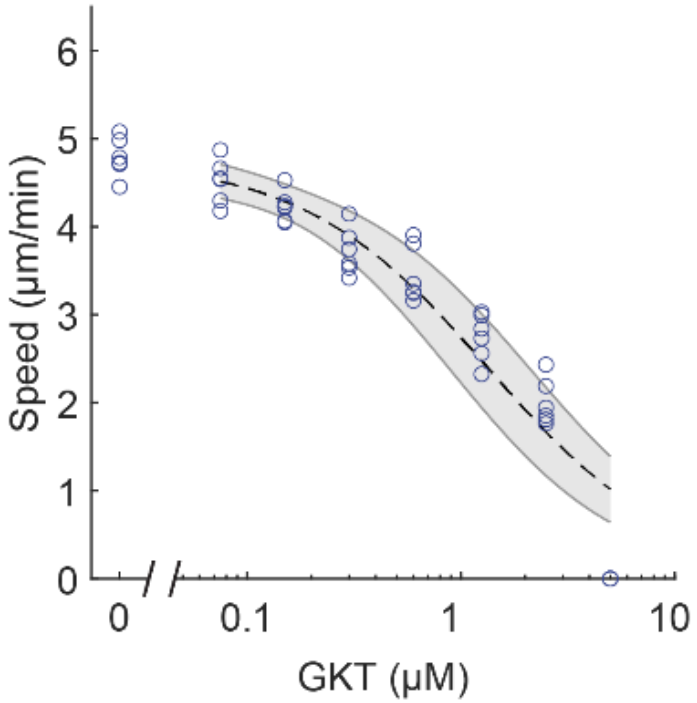


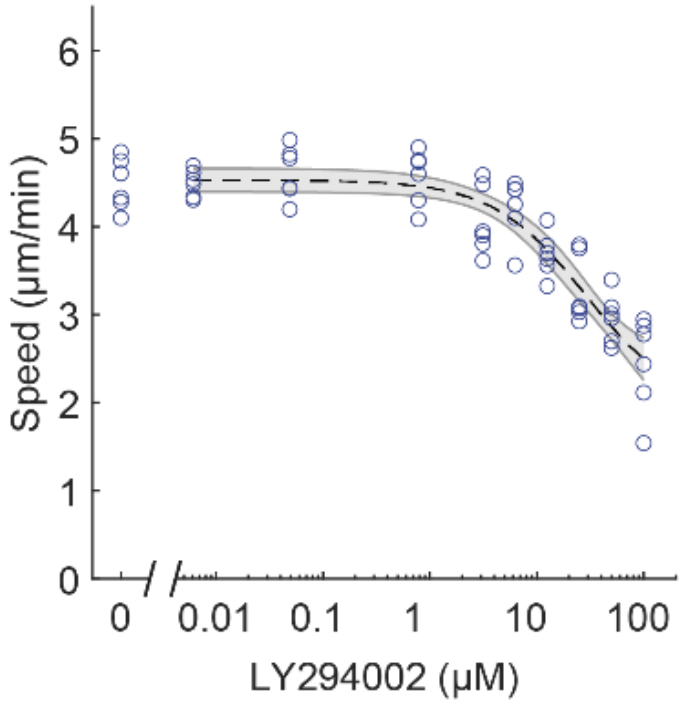
Wave speed changes dose-dependently with iron levels

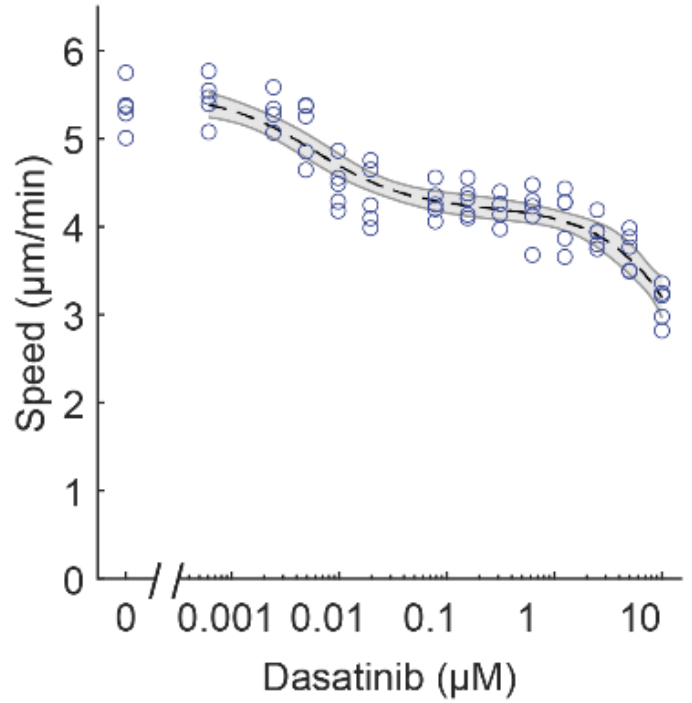


Wave speed changes dose-dependently with NOX feedback strength



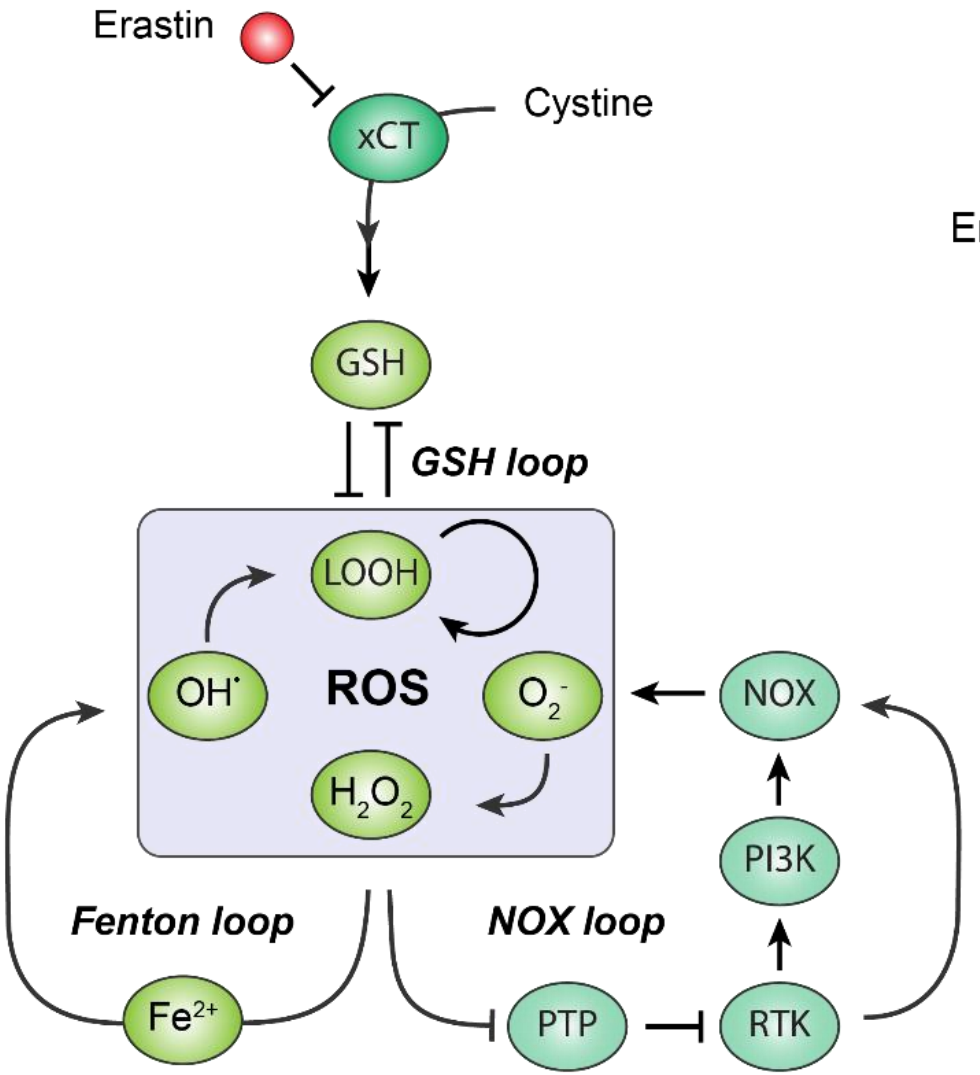


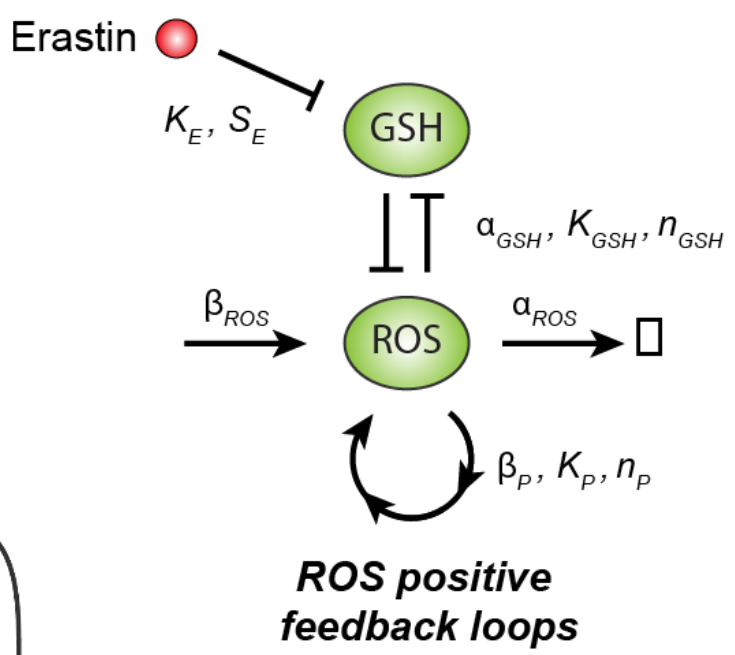




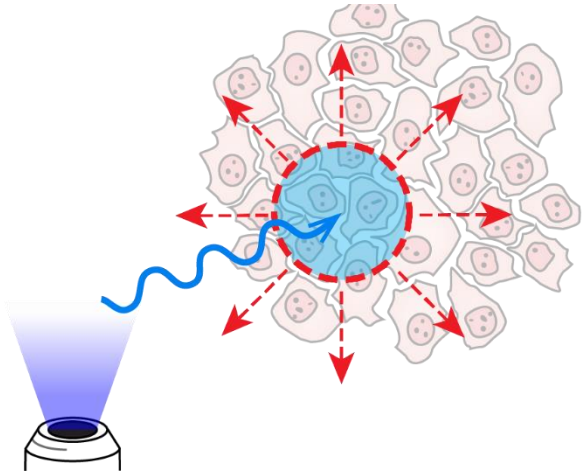
Can feedback loops lead to ROS bistable switch and ferroptosis propagation?

Multiple feedback loops in the ferroptosis regulatory network

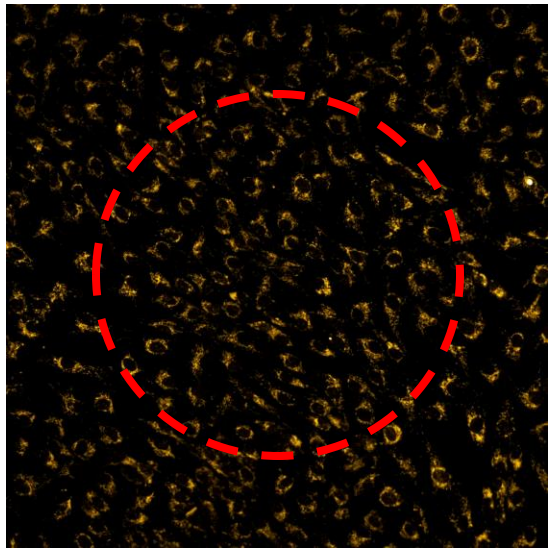




Experimental measurements of ROS bistability



Transient blue-light exposure



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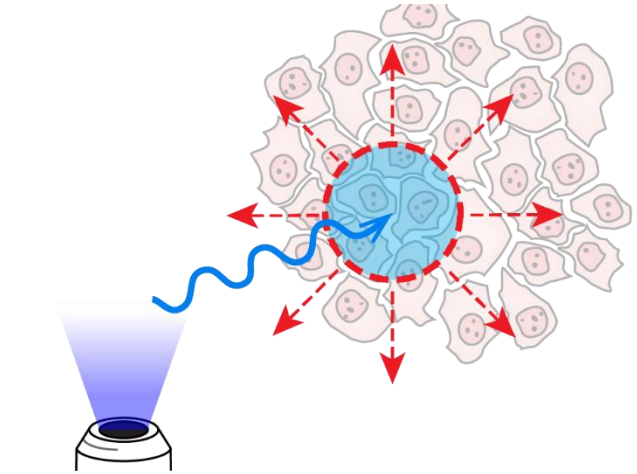
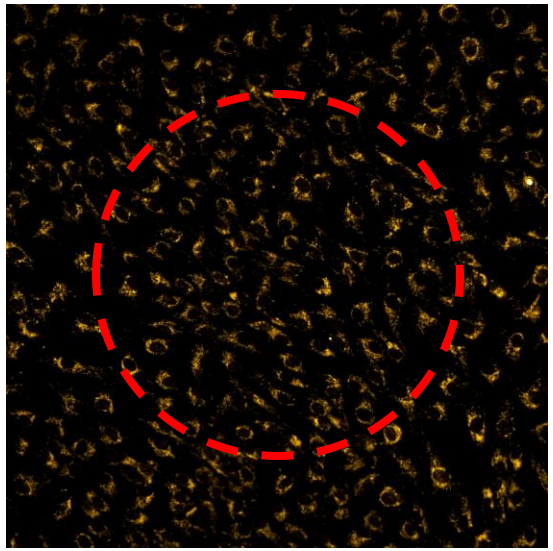
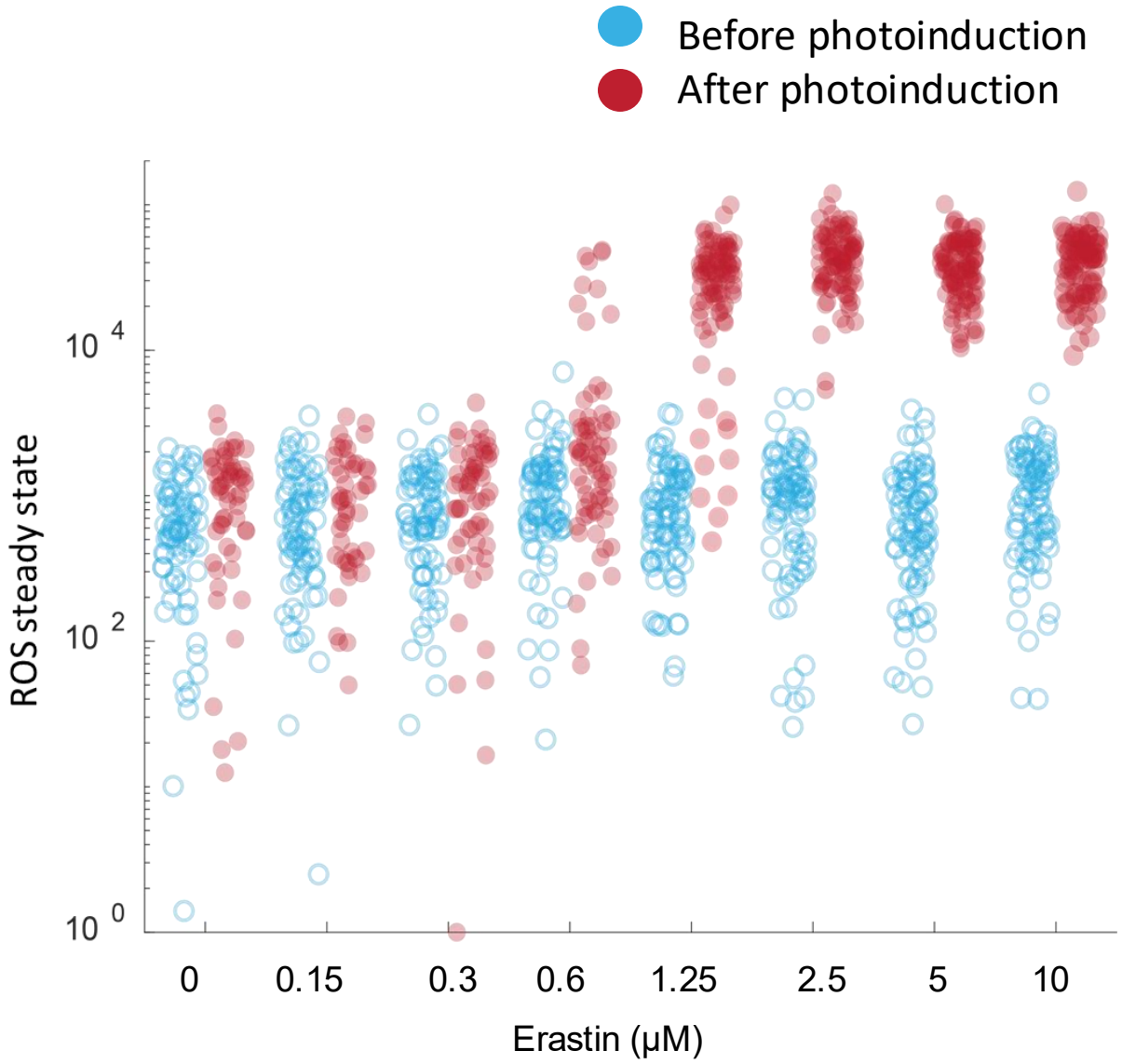


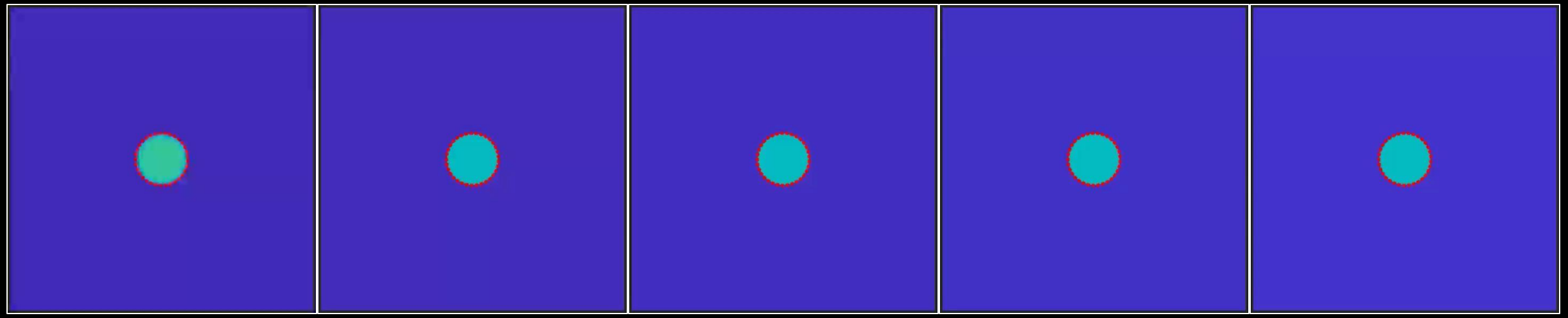
Transient blue-light exposure





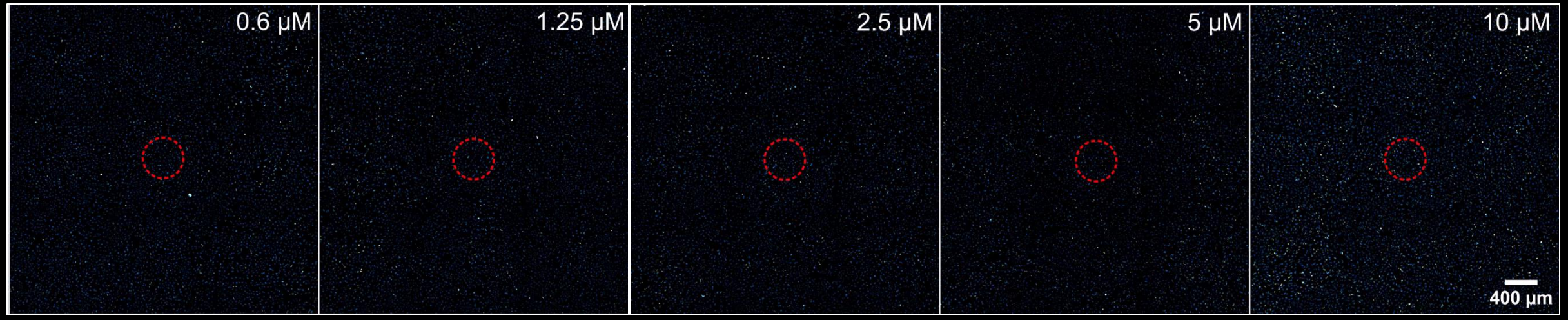
Ferroptosis stress quantitatively promotes ferroptotic trigger waves

Simulations



Experiments

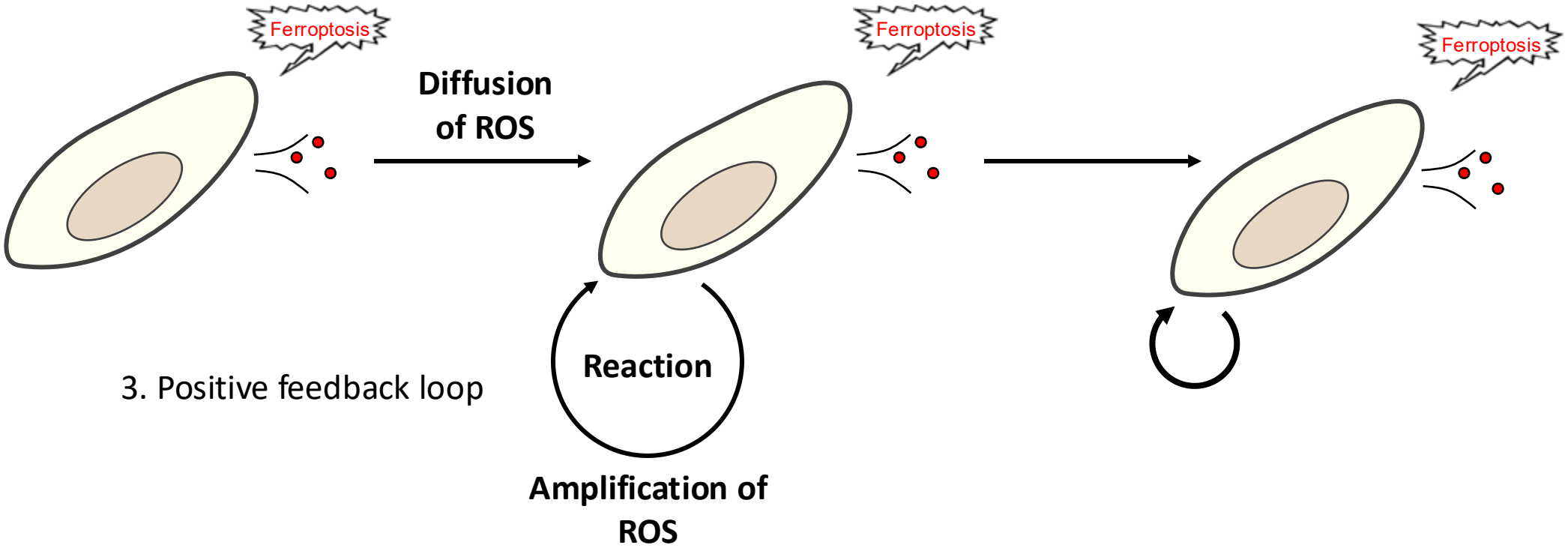
Erastin (μM)



Trigger wave model of ferroptosis propagation

1. Initiation point

2. Spatial coupling mechanism

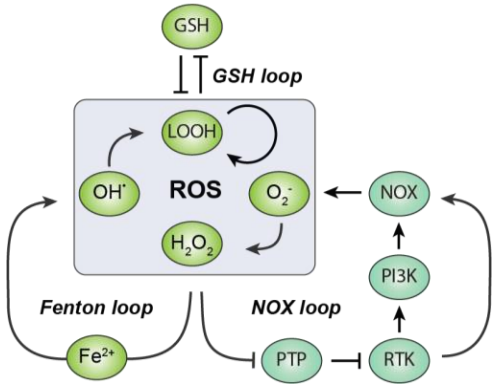


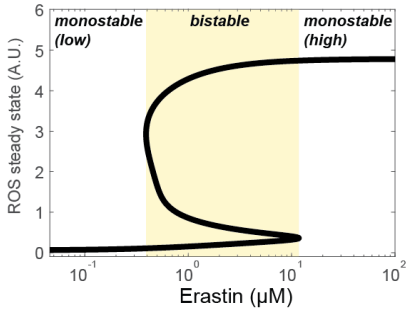
3. Positive feedback loop

Nutrient starvation primes cells for ROS bistability, causing large-scale ferroptotic cell death

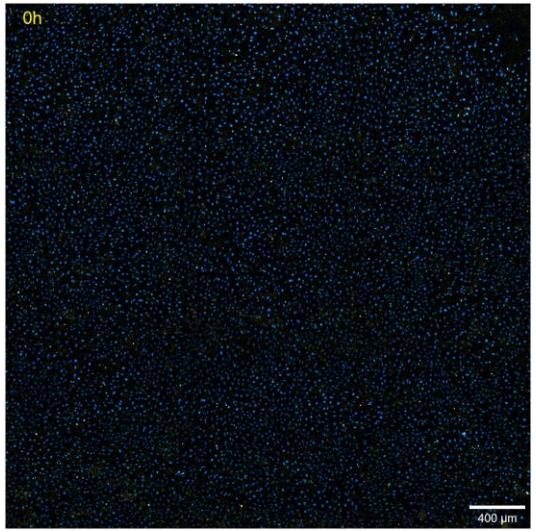
Priming signal → **ROS switch** → **Trigger waves**

- Nutrient (cystine) starvation





- Large-scale ferroptosis
- Long-distance ROS signaling



Do ferroptotic trigger waves occur *in vivo*?

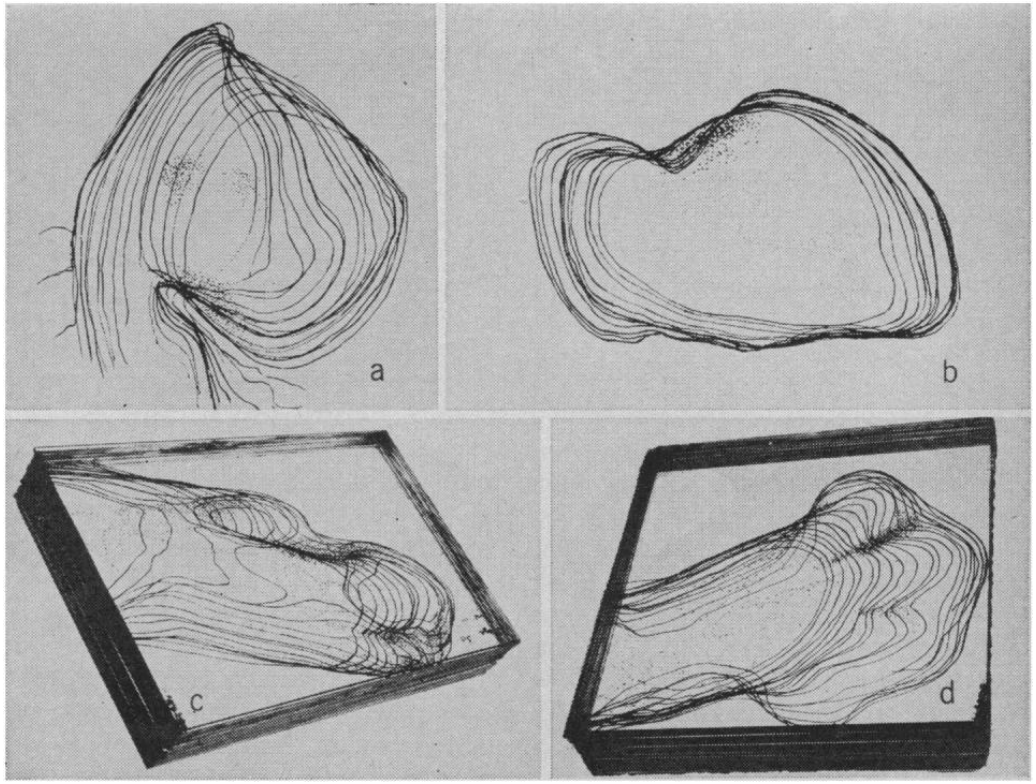
Cell death during embryogenesis

Death in Embryonic Systems

" Abundant death, often cataclysmic in its onslaught, is part of early development in many animals; it is the usual method of eliminating organs and tissues that is useful only during embryonic or larval life"

- John W. Saunders, Jr. (Science, 1966)

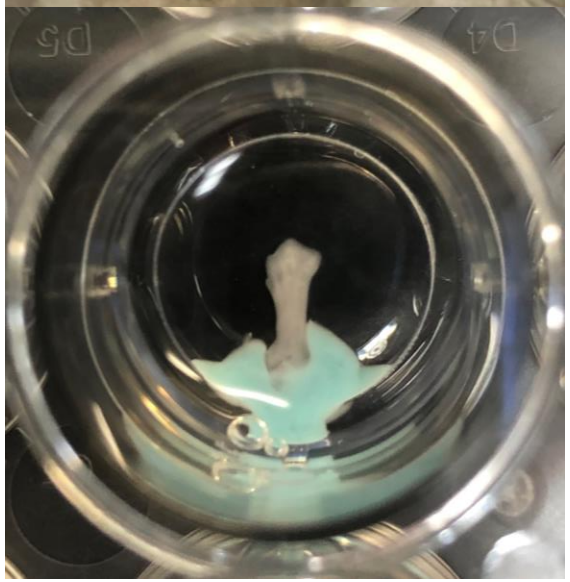
Does cell death spread as waves during embryogenesis?



”Sculpturing of the limb… follows closely upon waves of necrosis that sweep proximodistally along the mesoderm of the anterior and posterior margins of the limb”

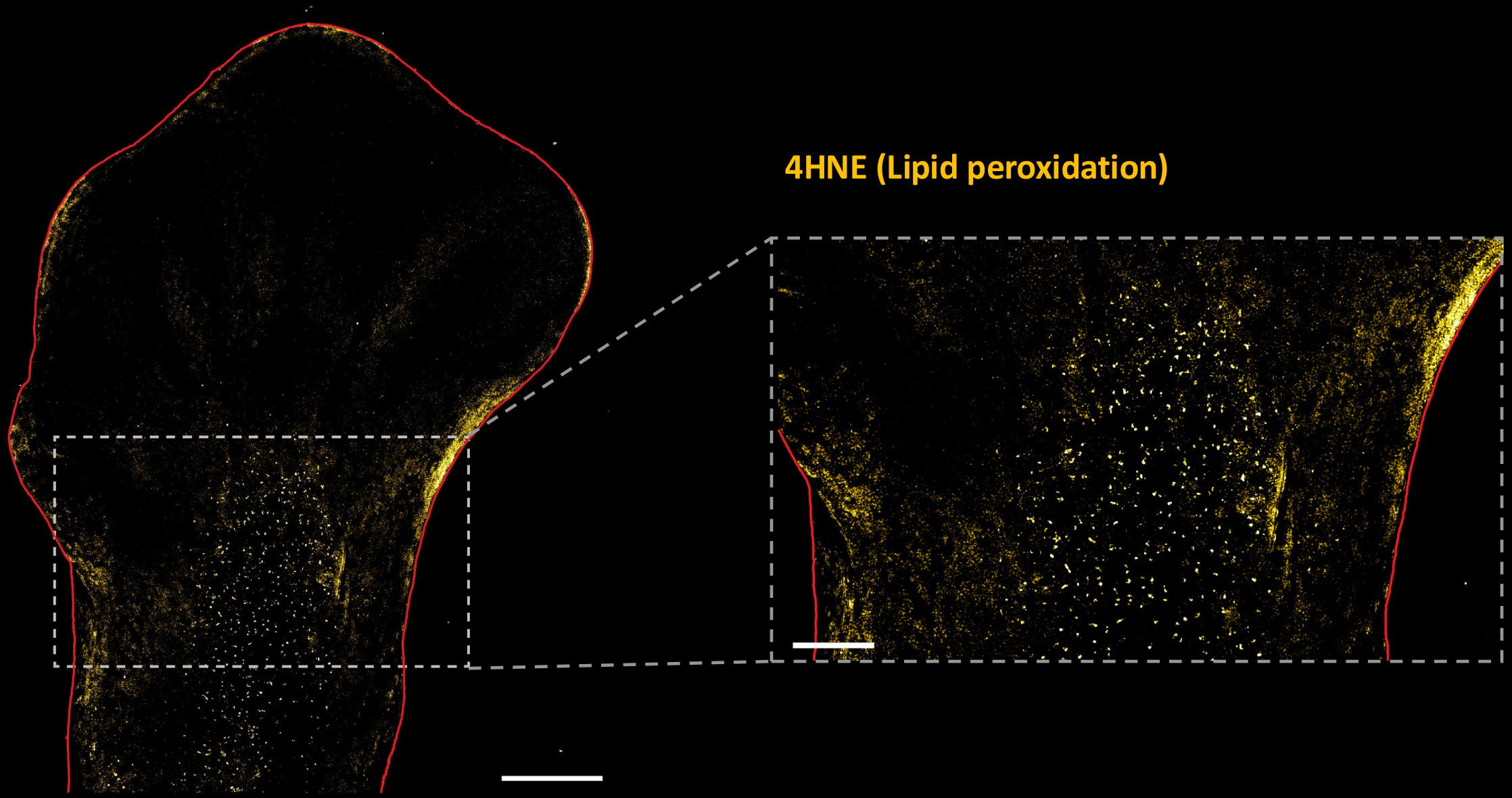
- John W. Saunders, Jr. (Science, 1966)

Sculpturing of the limb via cell death waves

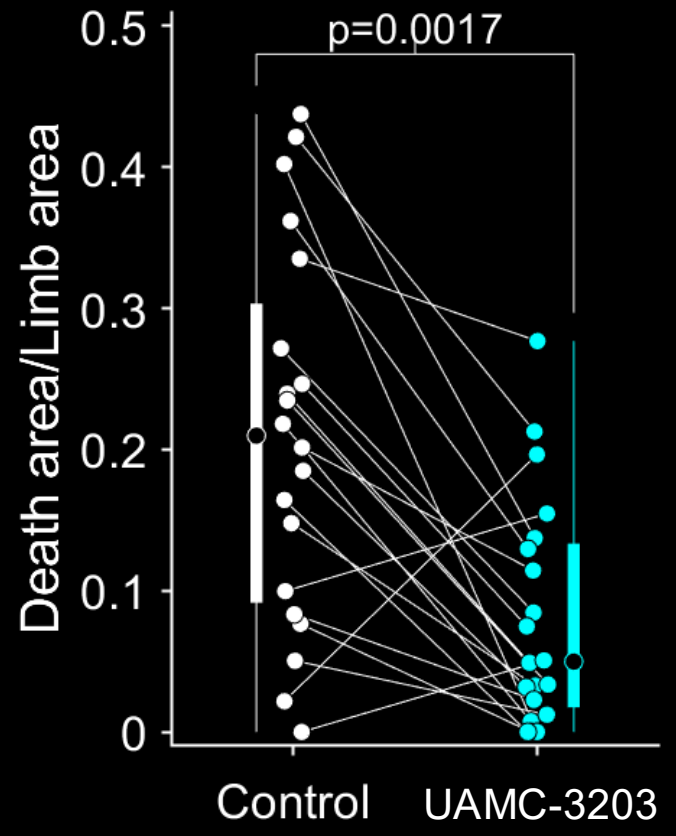


Hannah K. C. Co

Lipid peroxidation along the central area of the embryonic limb



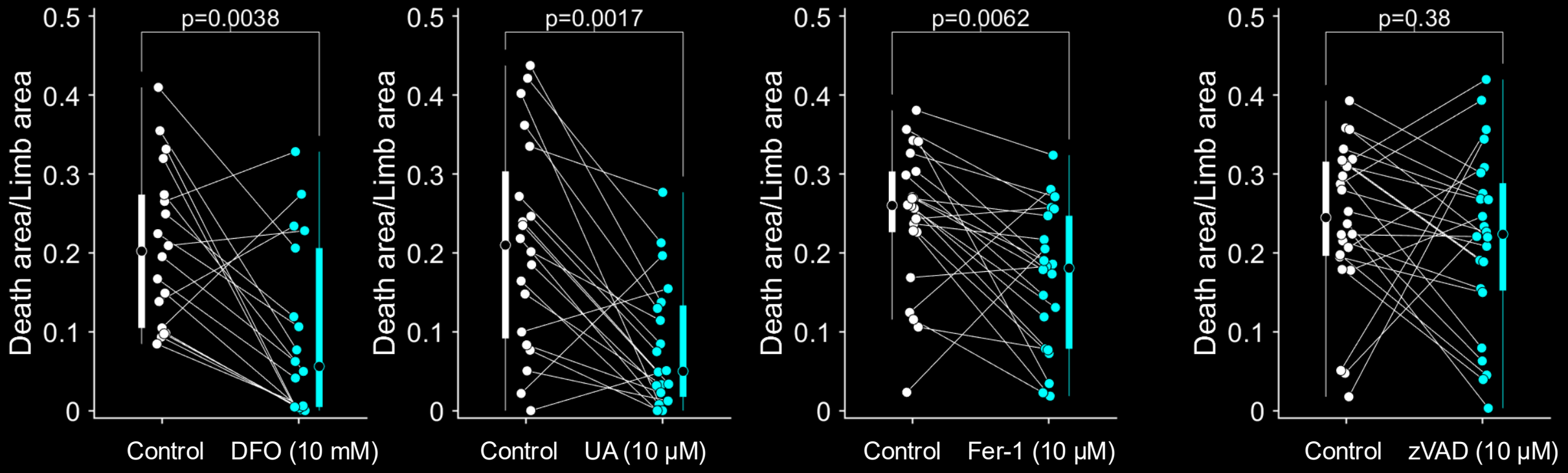
Cell death propagates along the central area of the embryonic limb



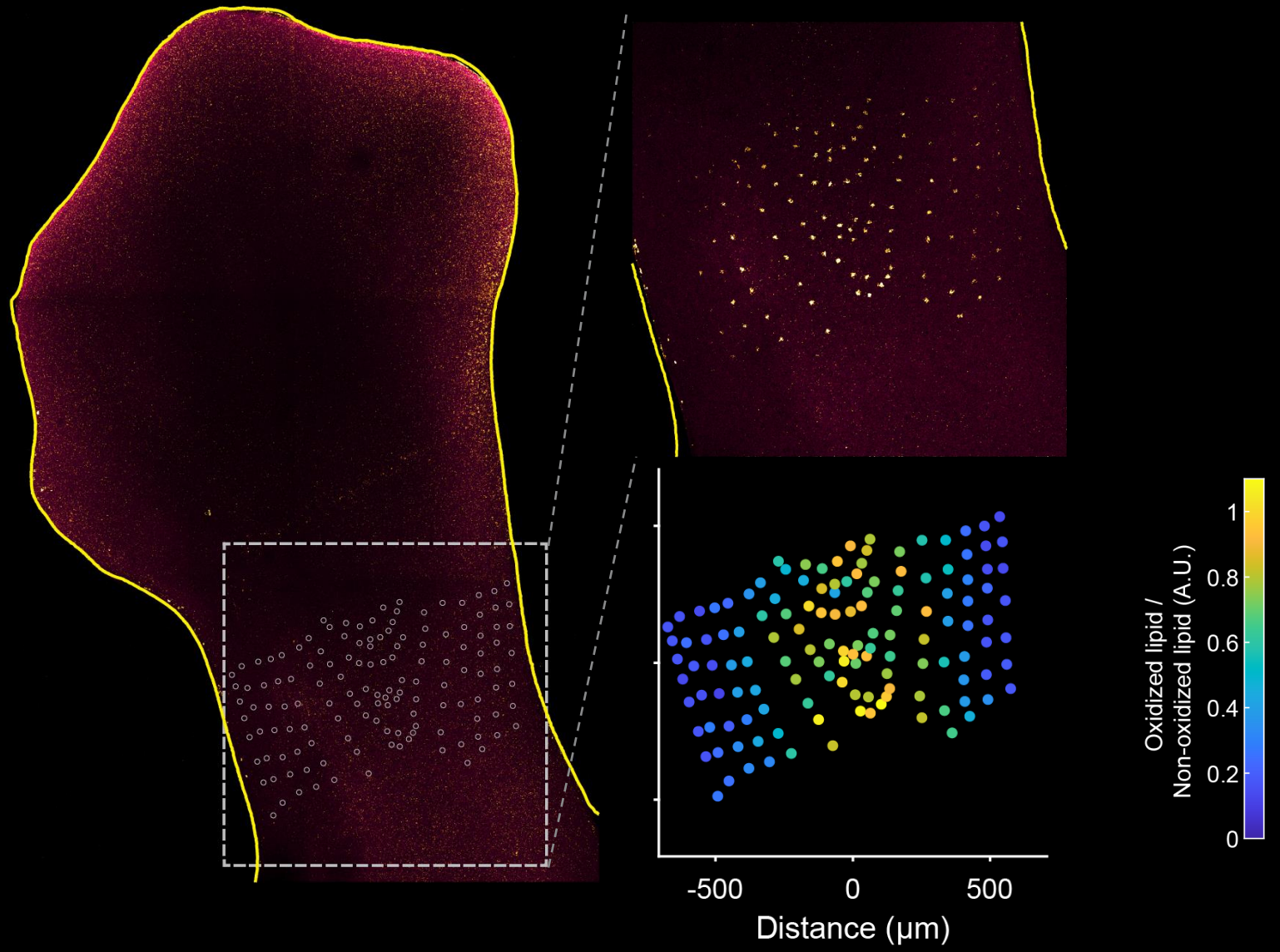
Apoptosis inhibitor do not suppress cell death waves in developing limb

Ferroptosis inhibitors

Apoptosis inhibitor

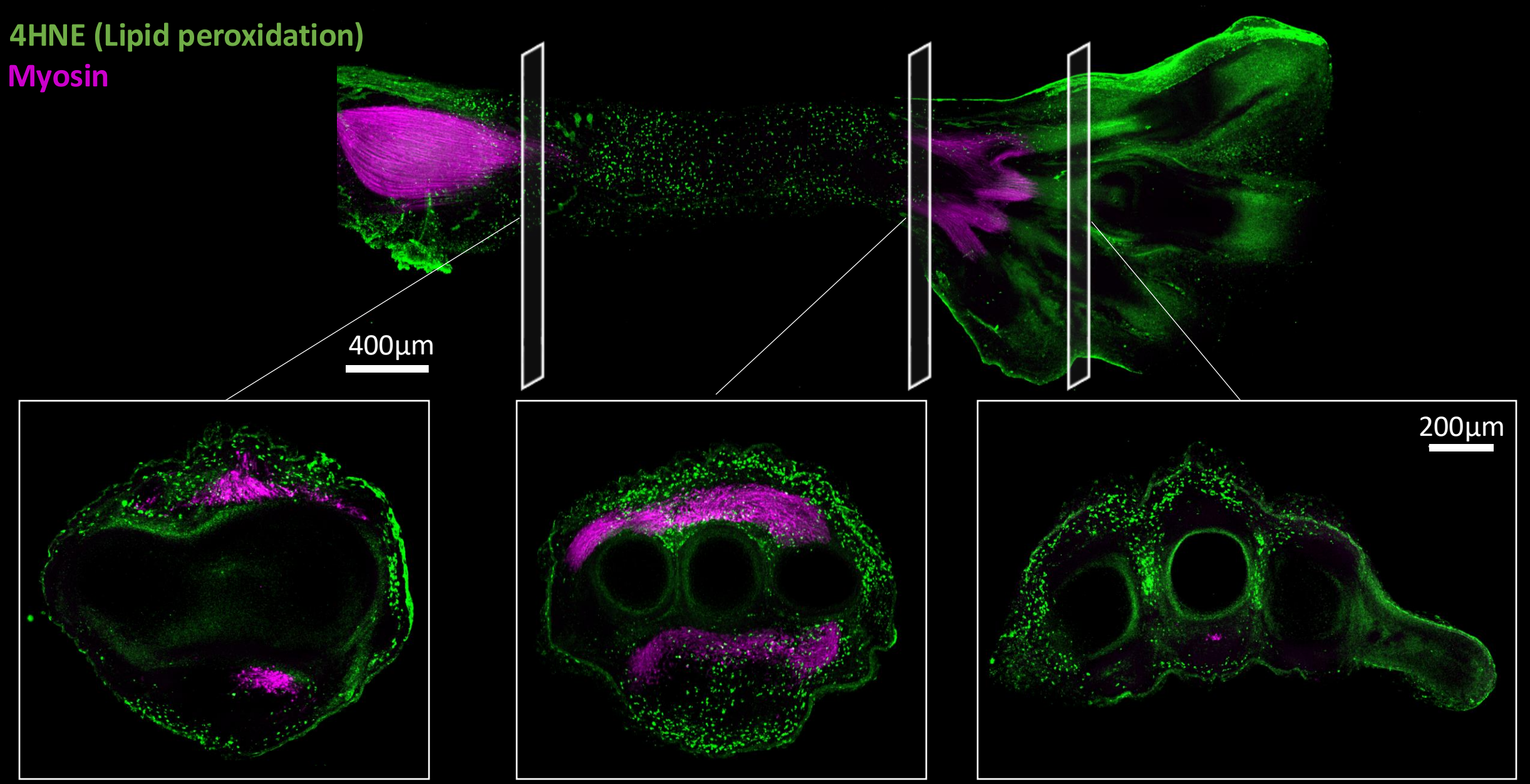


Oxidizable lipids (PUFAs) are higher at the central region of the limb



What is the function of ferroptosis during limb development?

Lipid peroxidation occurs in the developing limb



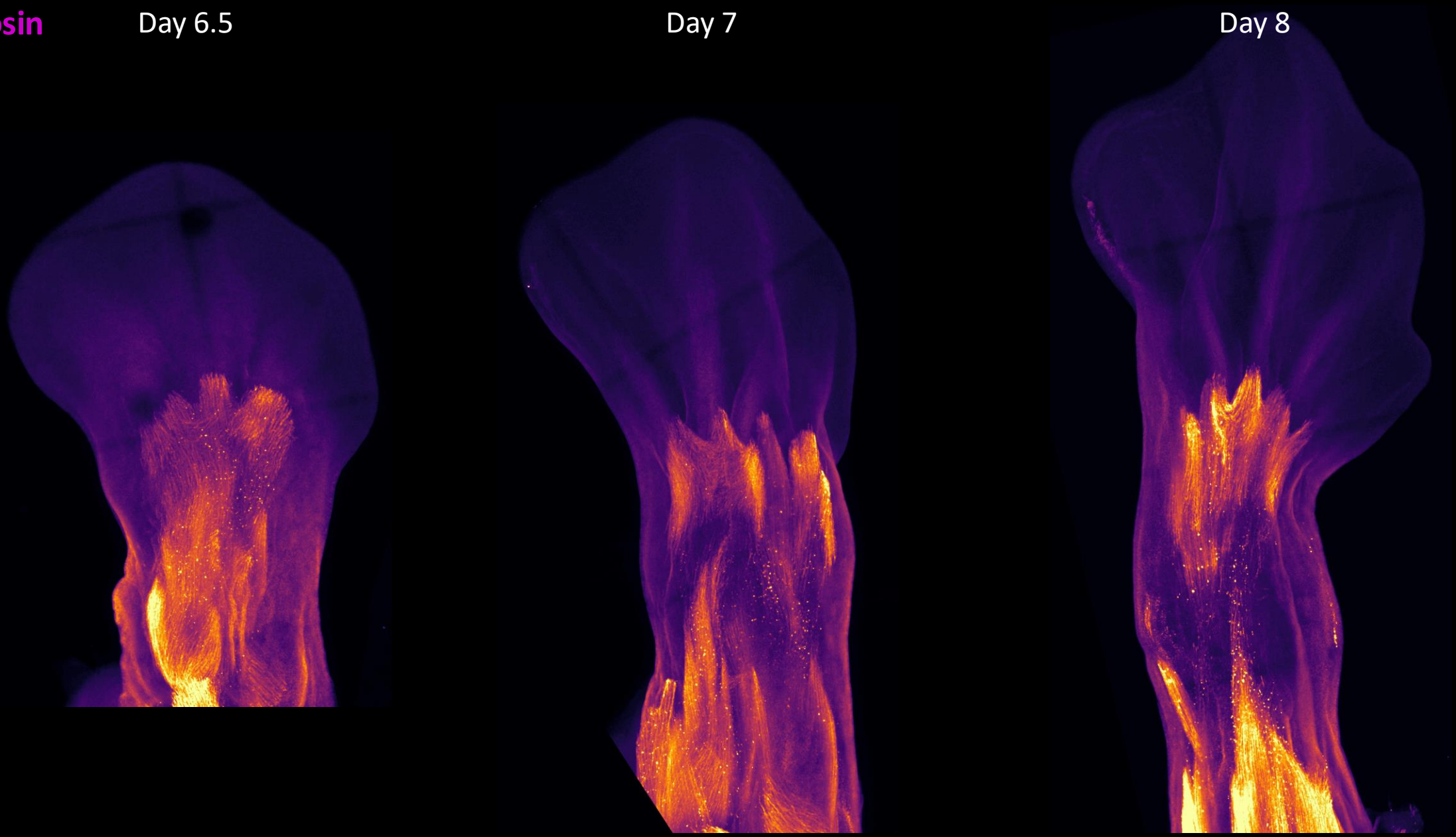
Muscle mass remodeling during embryonic development

Myosin

Day 6.5

Day 7

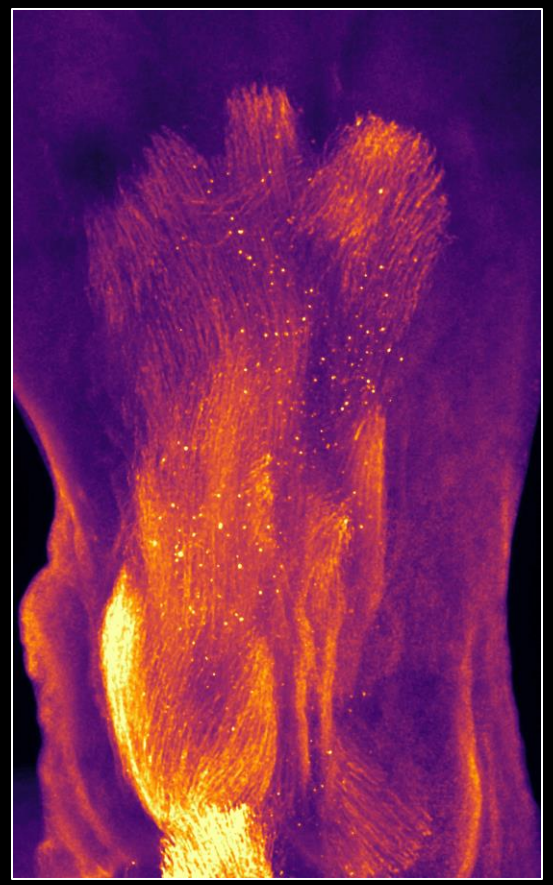
Day 8



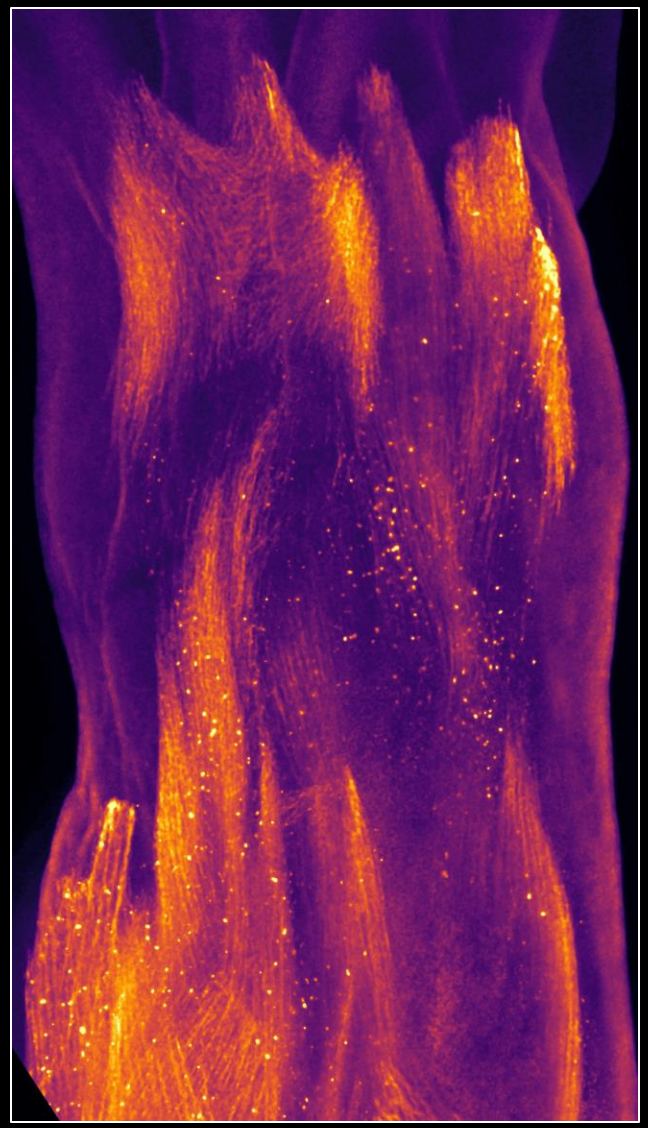
Muscle mass remodeling during embryonic development

Myosin

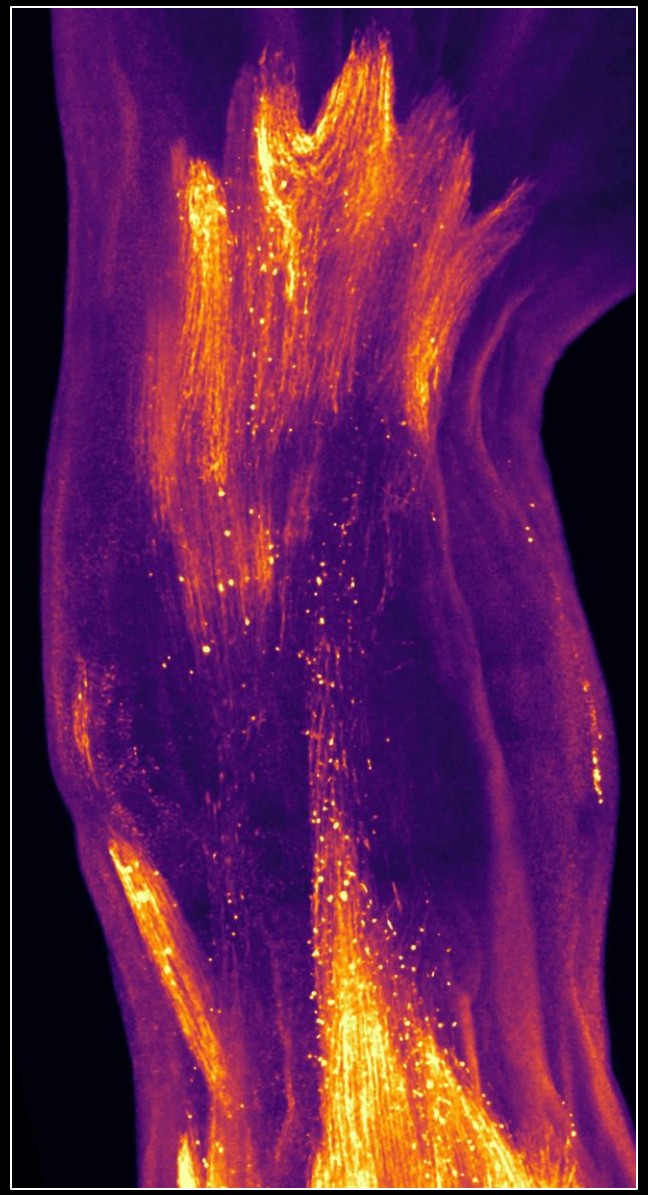
Day 6.5



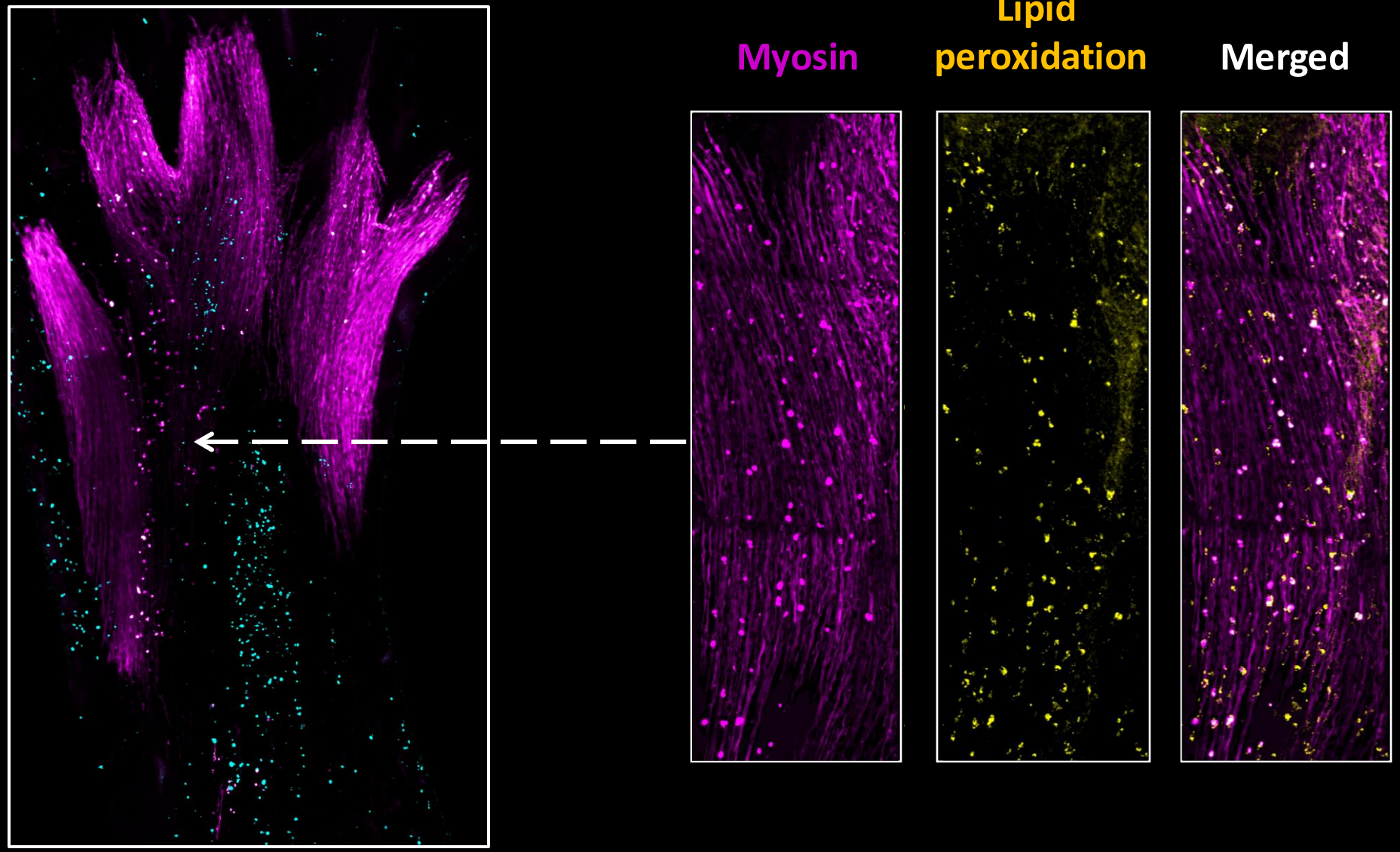
Day 7



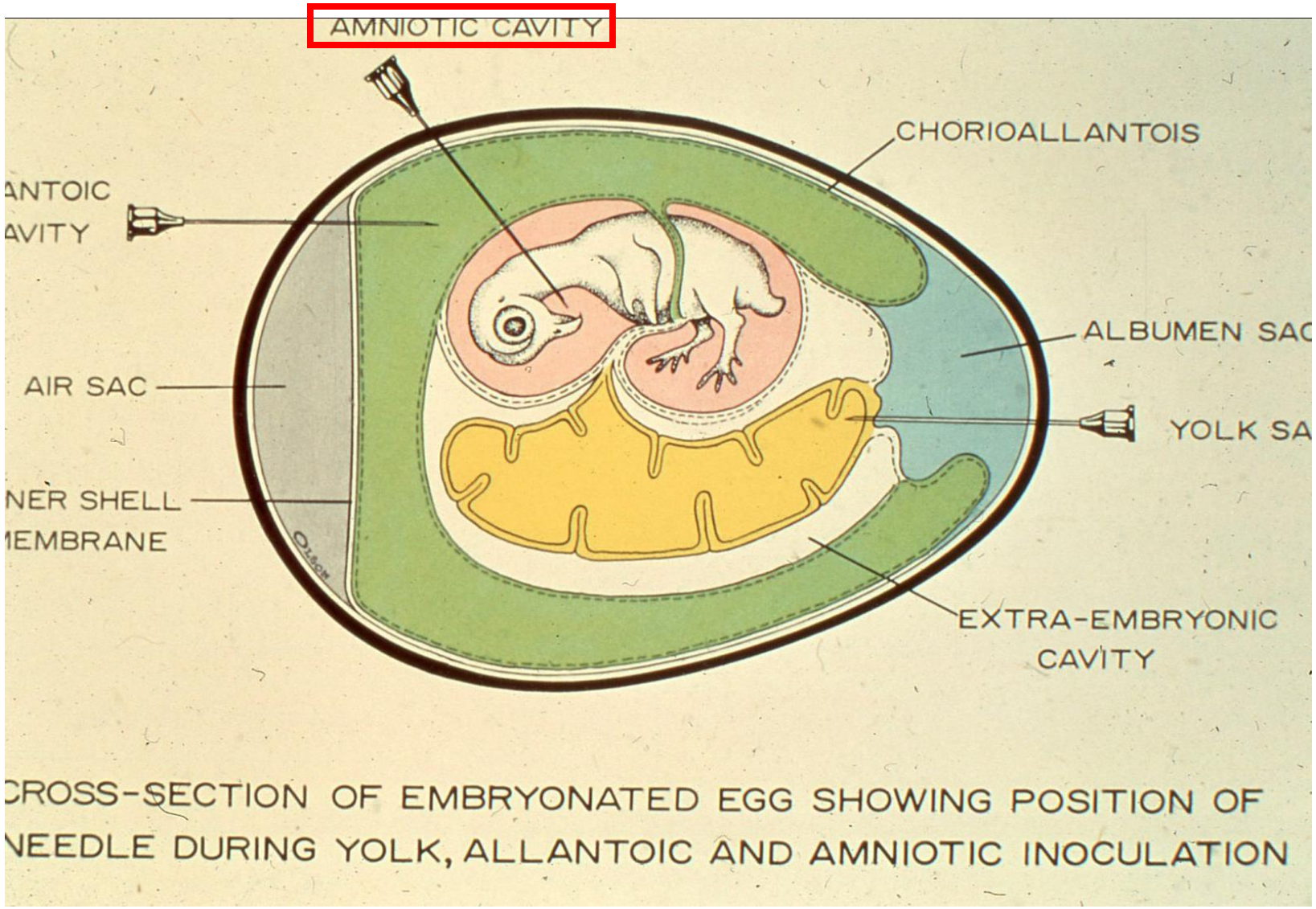
Day 8



Ferroptosis facilitates segregation of the muscle mass



Phenotypic characterization with amniotic sac injection



Amniotic sac injection of ferroptosis inhibitor

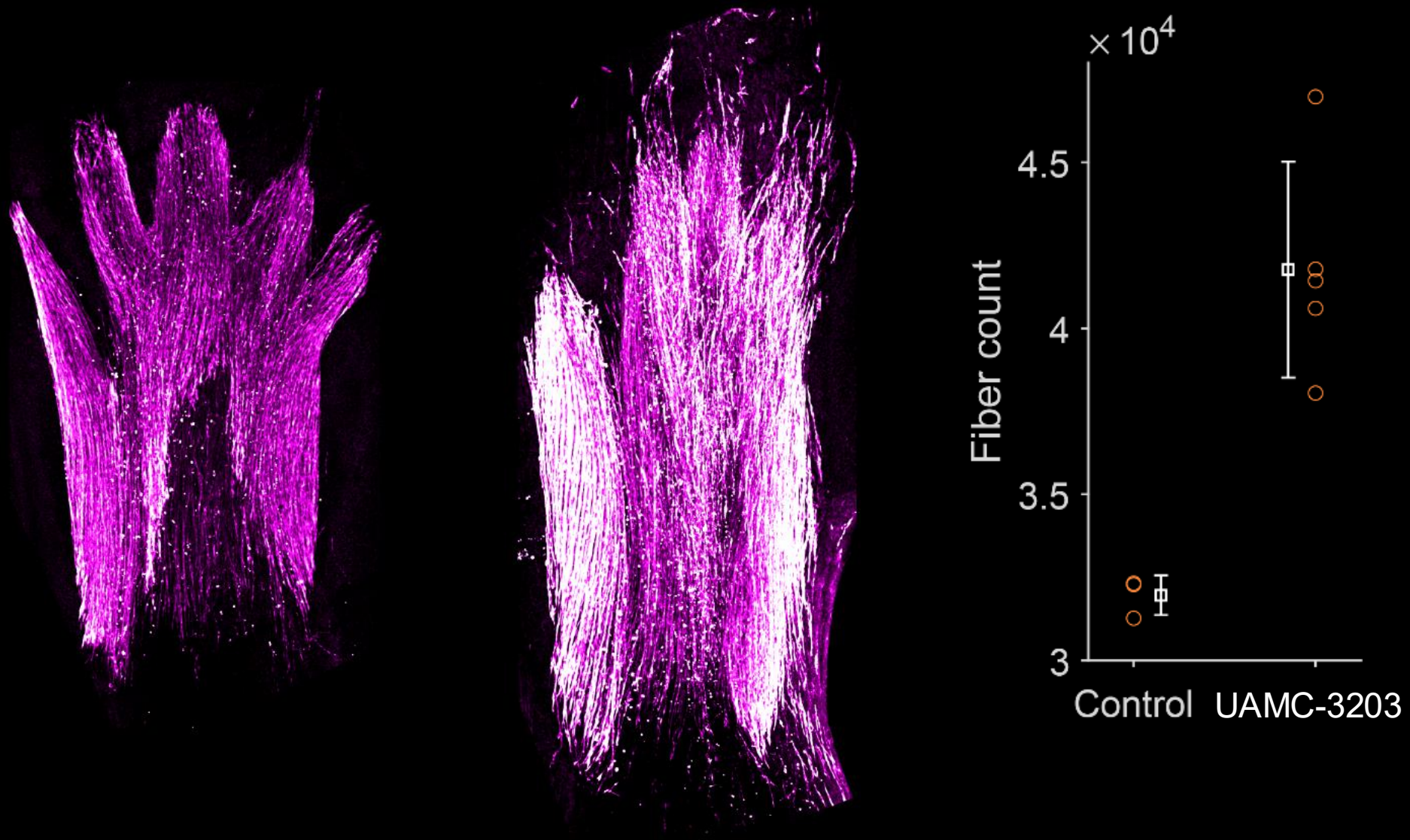
Candling

Injection

Alteration of muscle development under systemic ferroptosis suppression

Control (DMSO)

UAMC-3203

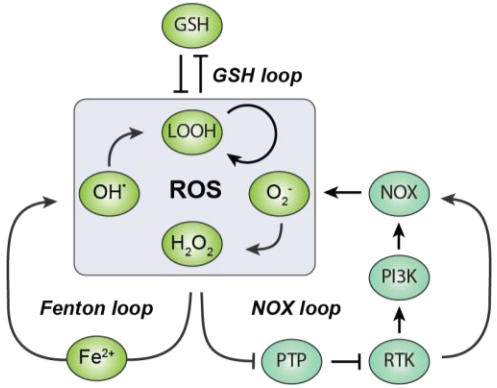


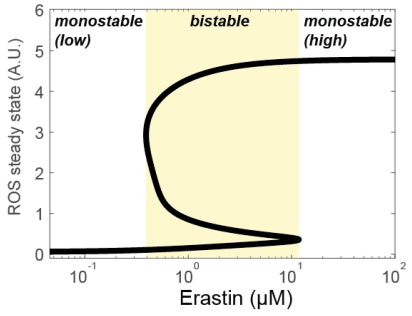
Central ectodermal cells as a temporary structure for muscle remodeling during limb development

Large-scale cell death via ferroptotic trigger waves

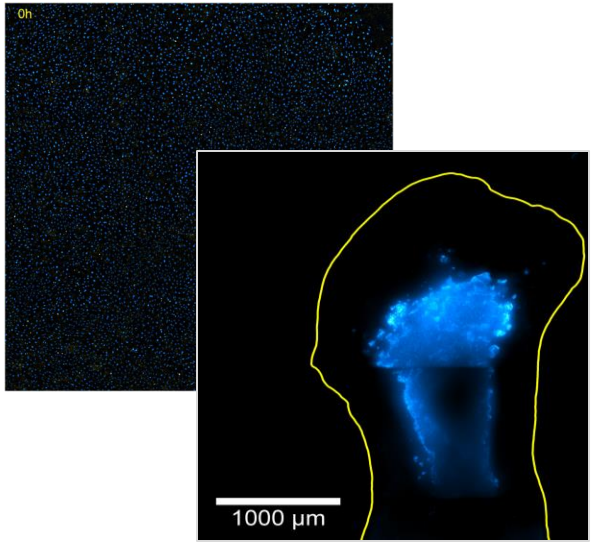
Priming signal → **ROS switch** → **Trigger waves**

- Nutrient (cystine) starvation
- Developmental signal, e.g., morphogens





- Large-scale ferroptosis
- Long-distance ROS signaling
- Tissue sculpturing

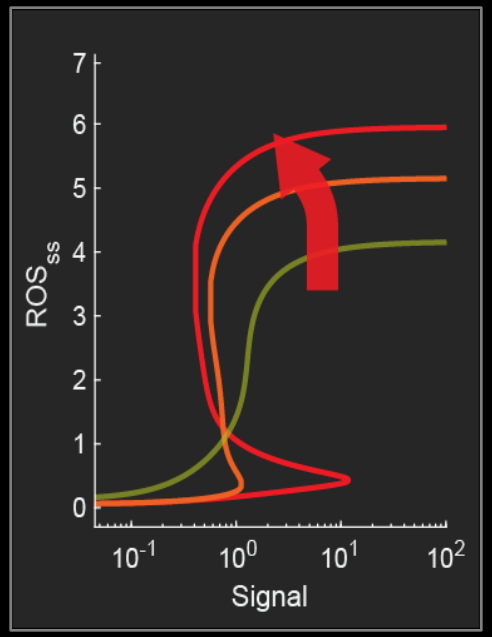


Future directions

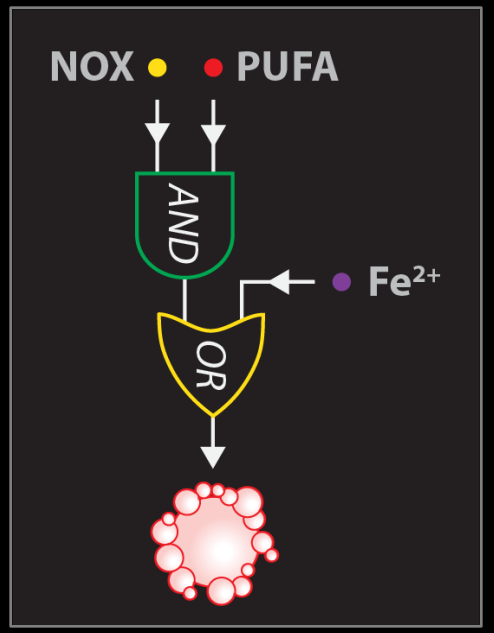
Priming signal → **ROS switch** → **Trigger waves**

Biological regulation of large-scale cell death

Behavior of ROS switches



Control of large-scale cell death



Acknowledgements

Funding

National Science Technology Council, Taiwan
National Taiwan University (AS-NTU joint Grant)
Academia Sinica (IMB, Career Development Award, Grand Challenge Seed Grant, Grand Challenge Grant)

Collaborators

Chih-hao Hsieh, PhD, NTU
Kyogo Kawaguchi, PhD, Riken
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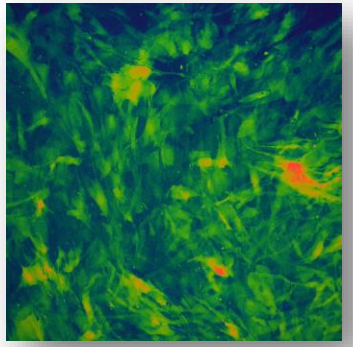
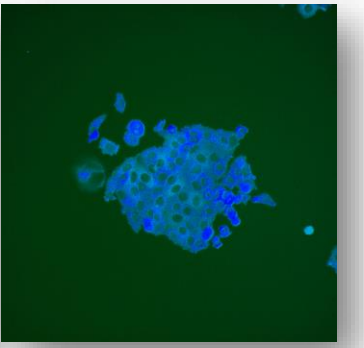
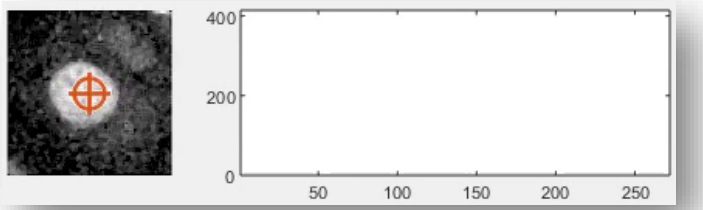
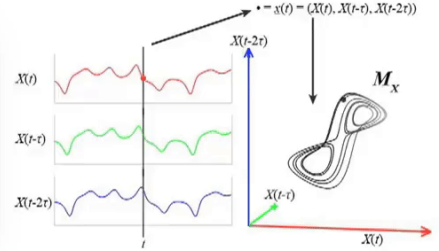


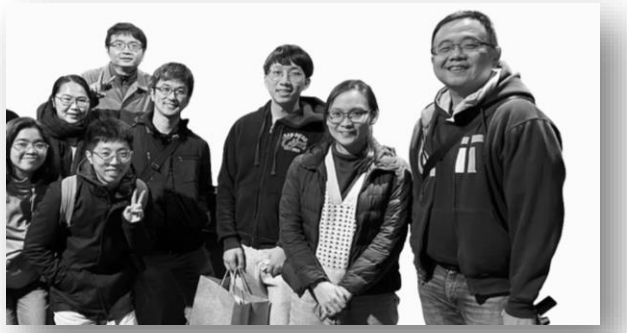



Ko-Wen Sun


Jen-Hao Cheng





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Shaping life via a series of cellular redox bombs

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通俗演講 Colloquium
May/13/2025