

Electrical, Chemical & Mechanical Excitable Networks in

Collective Cell Migration



Min ZHAO
Professor

Dermatology and Ophthalmology
University of California Davis School of Medicine



“...conservative estimates for total Medicare annual spending for all wound types ranged from \$28.1 billion to \$31.7 billion”

- Nussbaum et al., Value Health. 2018 Jan;21(1):27-32. doi: 10.1016/j.jval.2017.07.007. Epub 2017 Sep 19. An Economic Evaluation of the Impact, Cost, and Medicare Policy Implications of Chronic Nonhealing Wounds. 2014 data (Alliance of Wound Care Stakeholders)

Not real. simulation

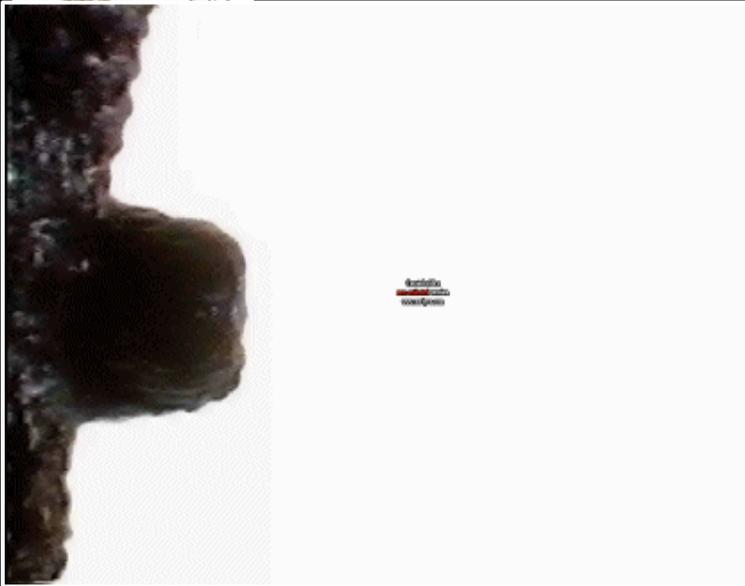


https://en.wikipedia.org/wiki/Battlefield_medicine

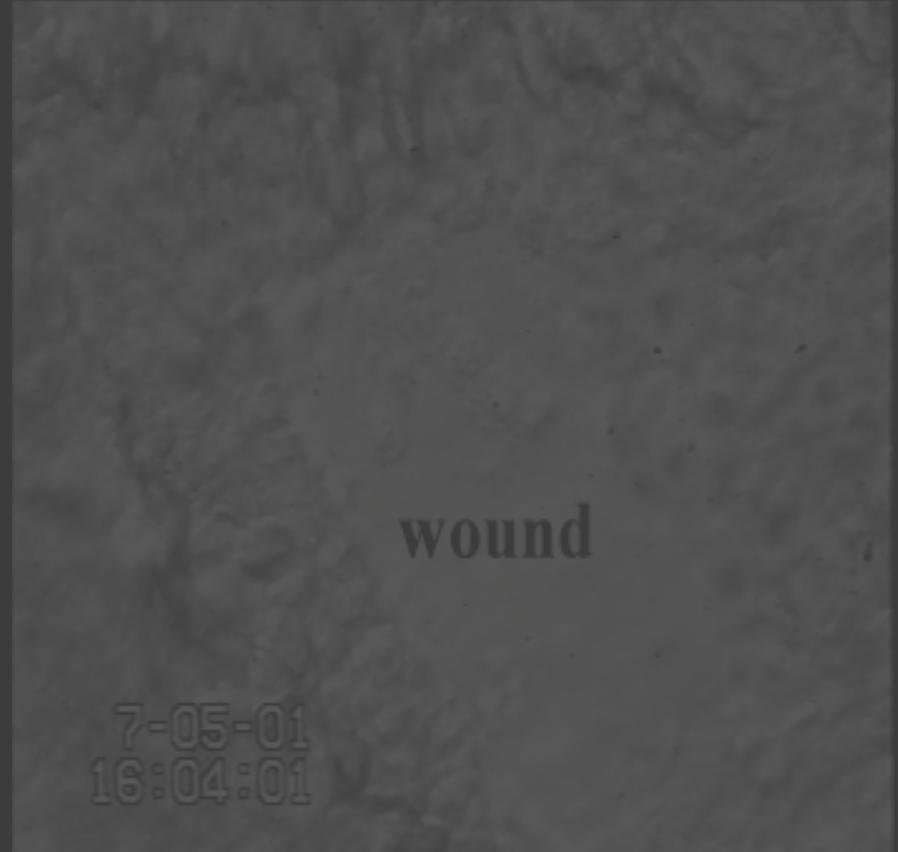
<https://ispr.info/2012/10/25/simulated-wounds-prepare-combat-medics-for-real-thing/>

The Management of Combat Wounds: The British Military Experience. ADV. WOUND CARE, 2016, 5(10).

Regeneration



100 μ m



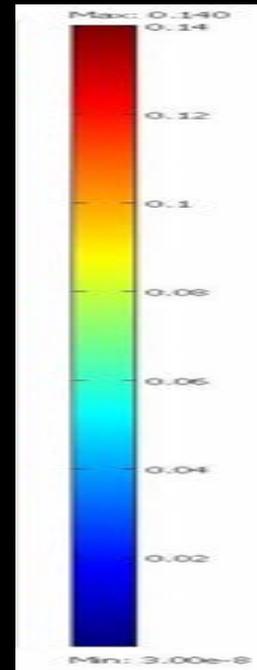
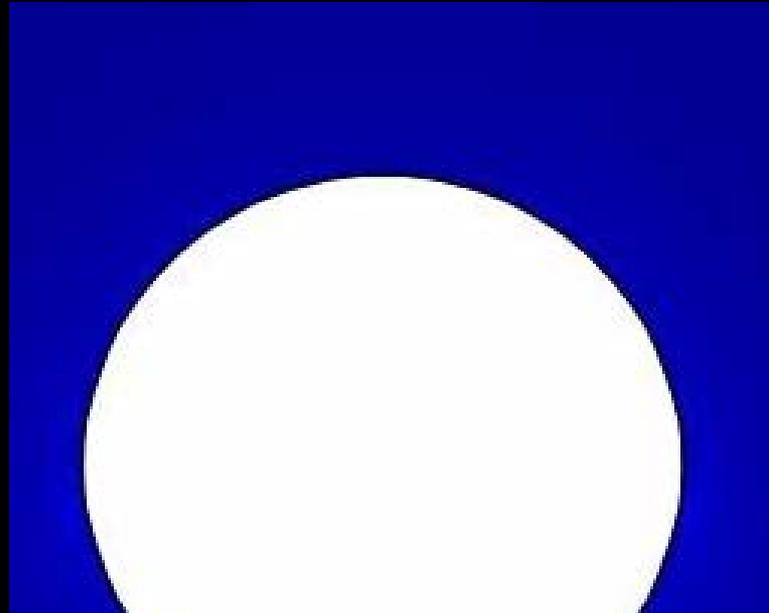
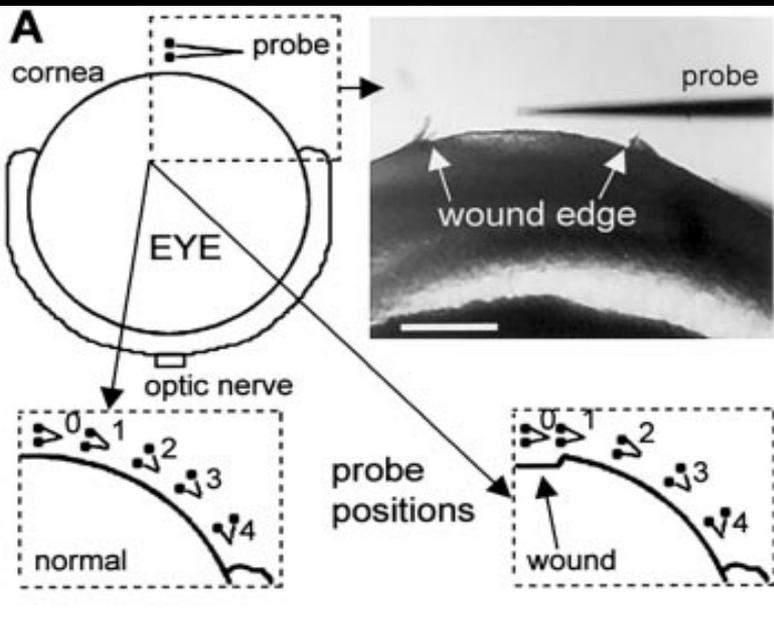
Excitable Networks

BioChemical: growth factors, cytokines, extracellular matrixes....

Electrical

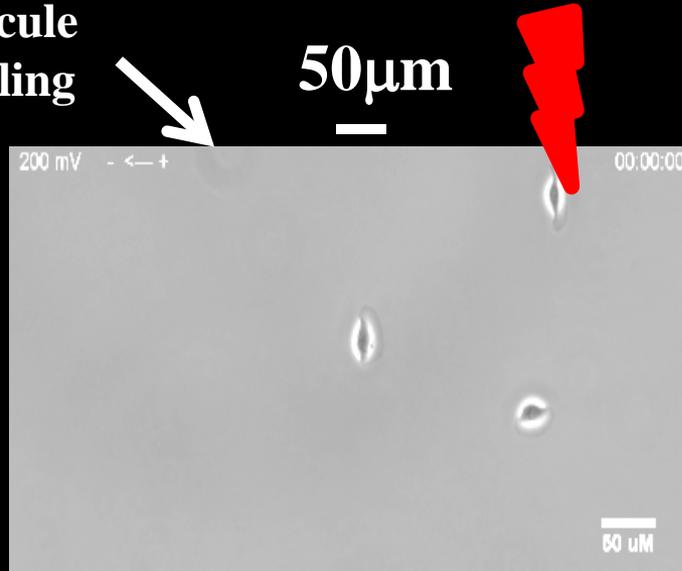
– wound itself naturally produce electric fields

Mechanical: stiffness and tension



how cells communicate within a group across all three BEM signaling modalities

Molecule
signaling



Electric field

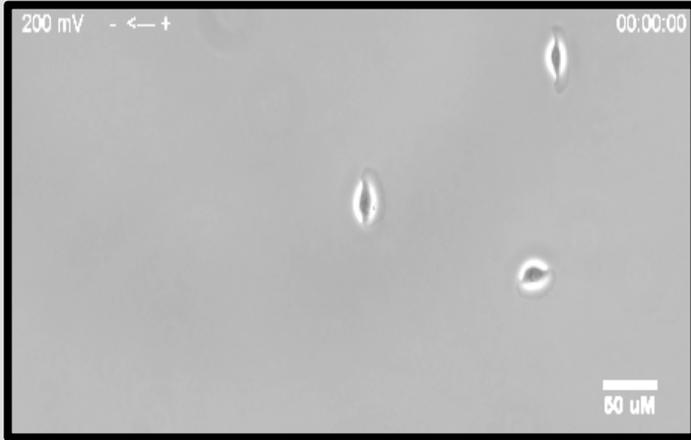
determines whether wounds close or open up.



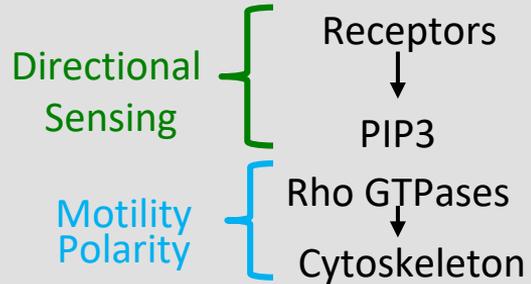
Significantly scaling up in size and time

1. two order bigger in the size
2. From minutes to up to 20 hours and days in the time

From signaling event at molecular level to
tissue behaviors

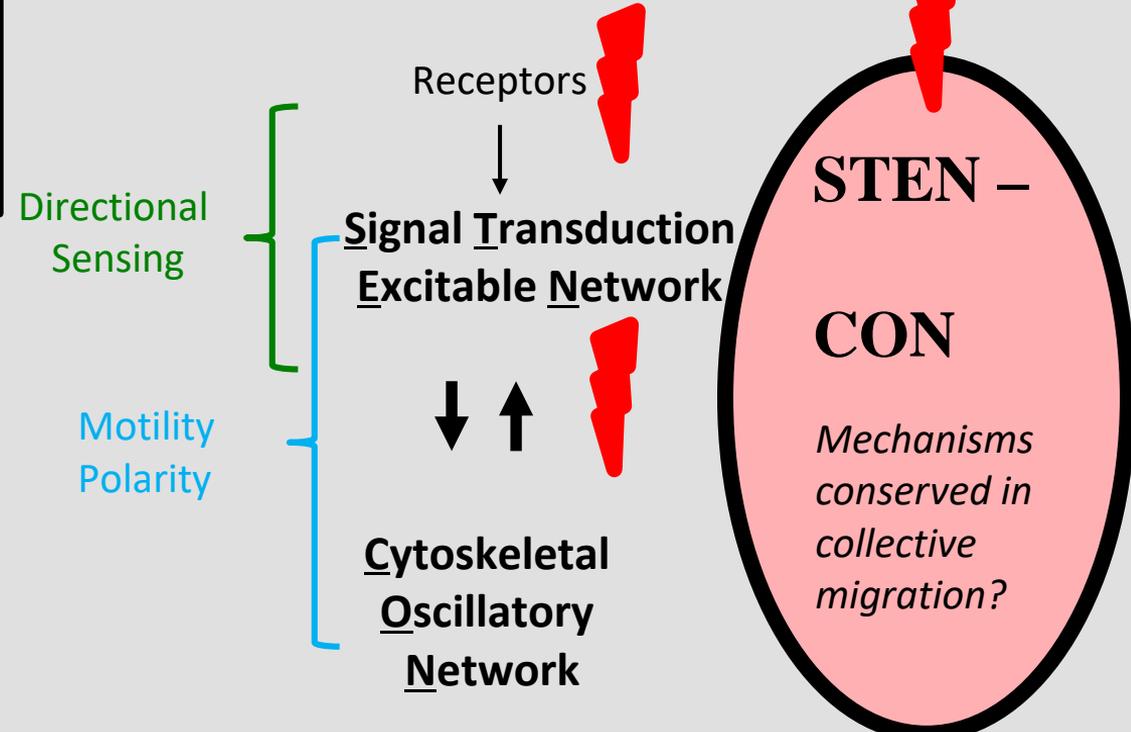


1998 Paradigm



Mechanism conserved in human cells

New Paradigm



Aims of this part of MURI

- **To understand how groups of cells sense and respond to electric stimuli**
- **To electrically coordinate multicellular functions**

MURI team

Wolfgang Losert (UMD), Quan Qing (ASU), Peter Devreotes (JHU)

Brian Reid

Fernando Da Silva Ferreira , PhD Candidate

Dr. Yaohui Sun



Volodymyr Ryzhuk, MSc



Kan Zhu



Liang Guo

Dr. Yan Zhang

Morgan Trexler
John Albeck
Ahmed Hassan
Cheng-Ming Chuong
Robert Chow

Over all synergy

Devreotes Lab at Johns Hopkins

EF-regulated intracellular signaling pathways

Losert Lab at Maryland

EF-regulated ERK activation and actin polymerization in epithelial cells

Qing Lab at ASU

Advanced electrical stimulation device and application

Expanding and extending to

Army Project (JAP, Dr. Trexler) Electrogenic biomaterials for severe cornea wounds
(DoD #W81XWH-14-1-0542)

Other collective cell behaviors – NYU, USC, Oxford University (England)

Single cells

1. Epithelial cells show similar response

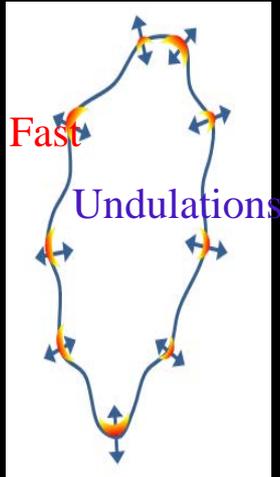
CON – cytoskeletal oscillation (membrane)

STEN - signaling induced large protrusion

(with Alex Mogilner, NYU)

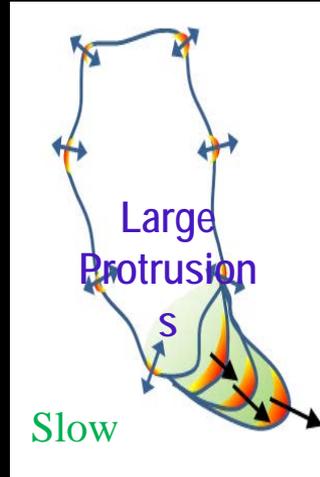
CON

(Cytoskeletal
Oscillatory Network)



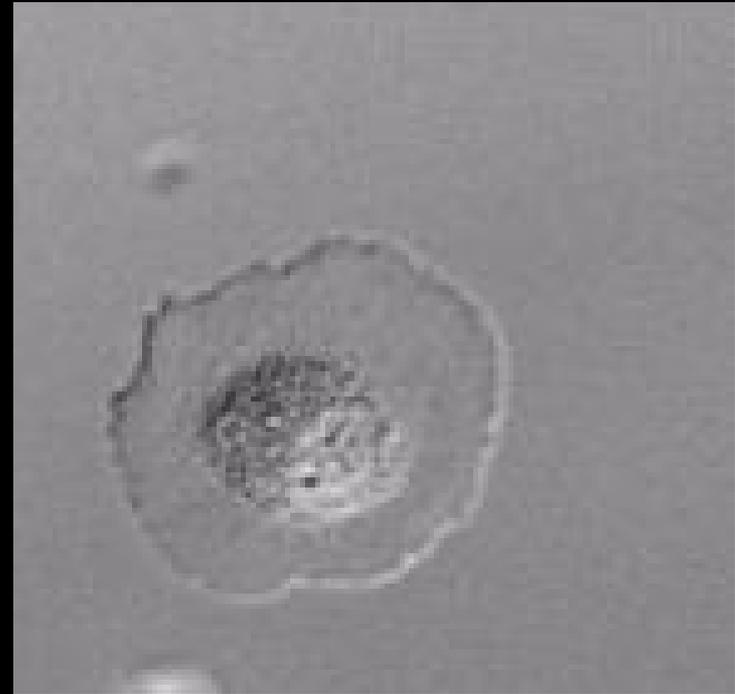
STEN

(Signal Transduction
Excitable Network)

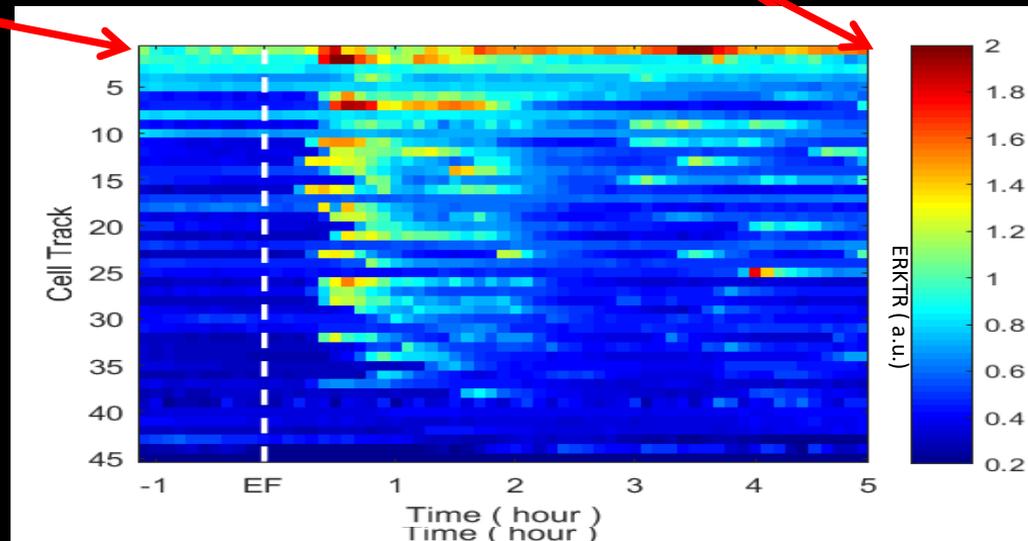
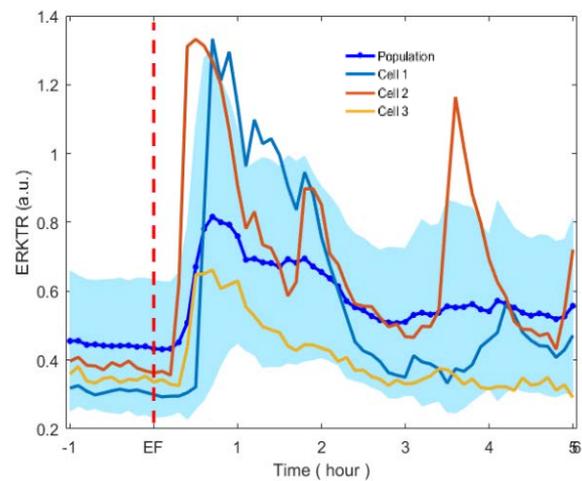
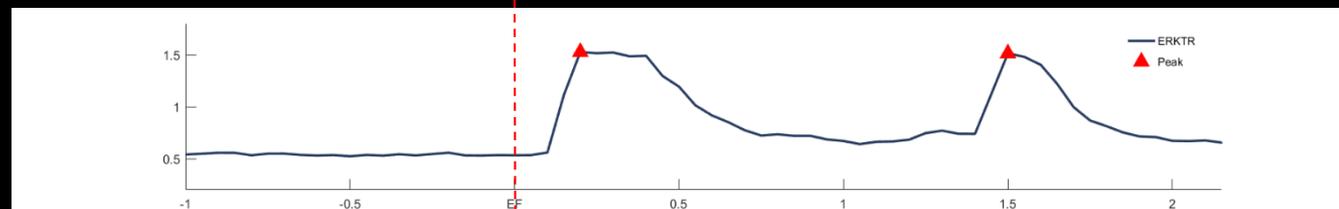
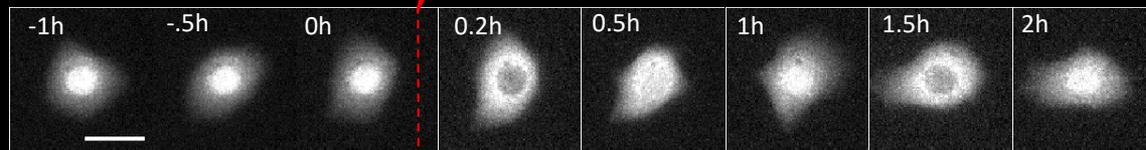


20 μm

00:00

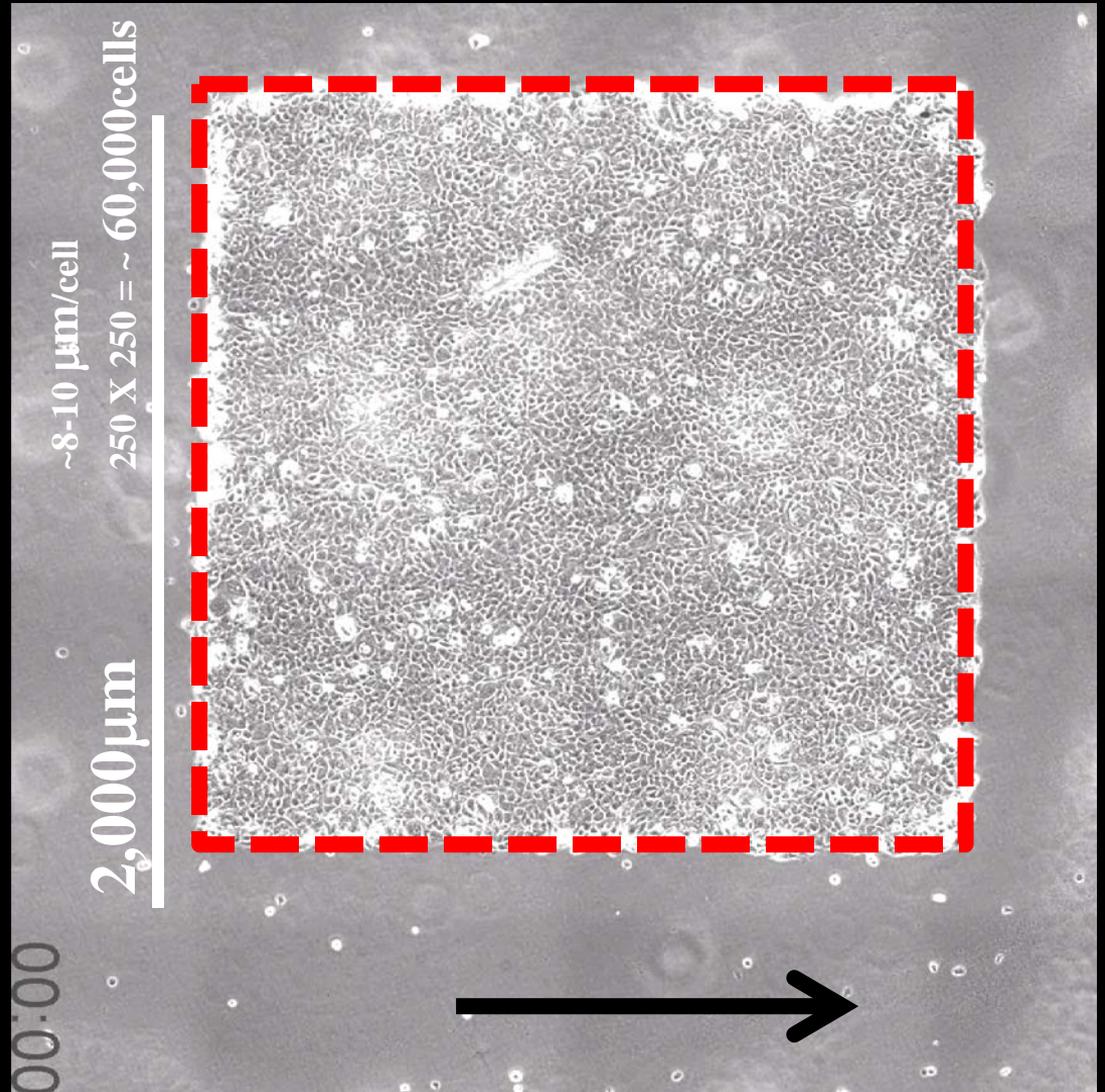


DC electric fields activate ERK



**2. Cell sheets
respond to EF by
collective
directional migration.**
(with Pan lab at UC Davis)

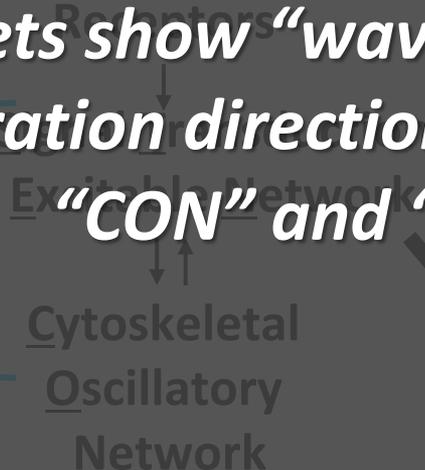
7 hours



New Paradigm

3. Cell sheets show “wave propagation” in migration directionality and speed similar to “CON” and “STEN”. (Losert Group)

Directional Sensing
Motility Polarity



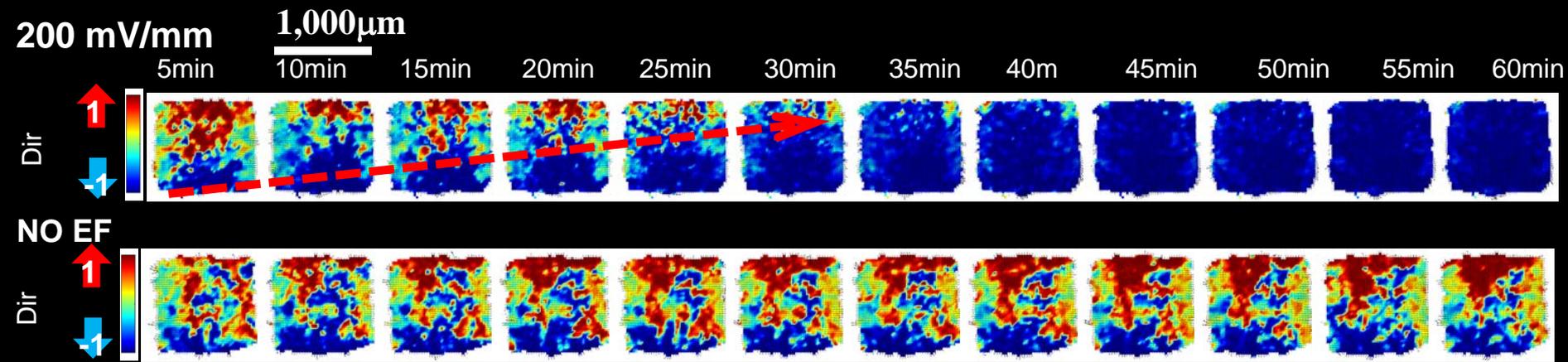
Quantitative analysis of Migration

Cytoskeletal dynamics

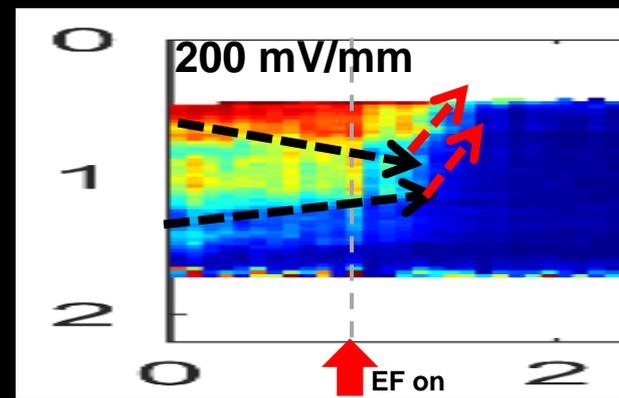
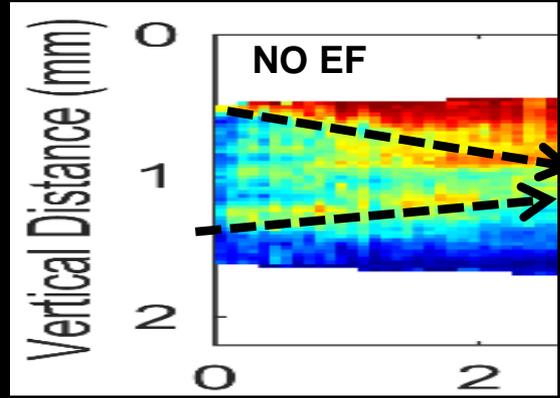
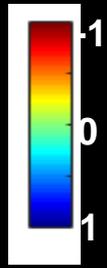
Signaling dynamics



• EF overrides the migration directionality wave.



Directionality



4. Probing into the intracellular cytoskeletal networks signaling pathways

Collective cell
migration

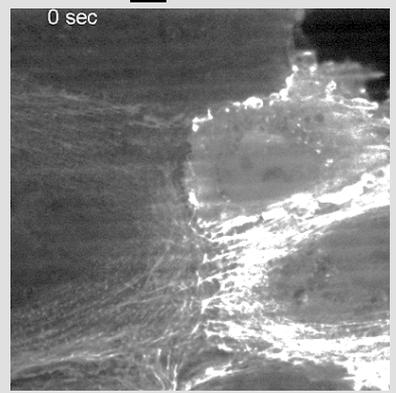
(*Quan Qing Lab, ASU; Losert Lab, MDU; Devreotes, JHU;*
John Albeck lab, UC Davis)

Polarity

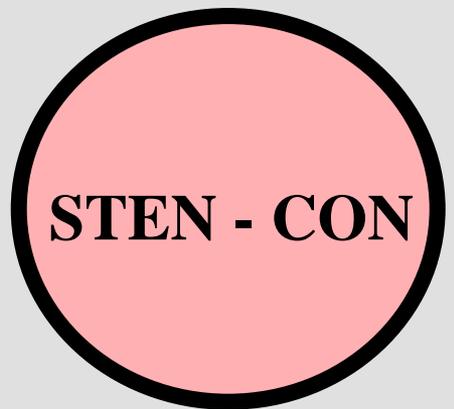


Collective
Migration

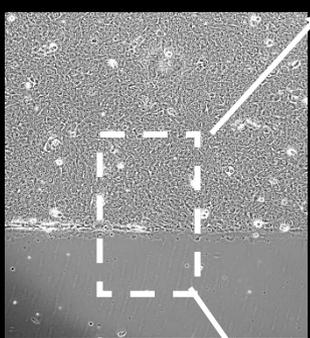
Cytoskeletal
Oscillatory
Network



Signaling
Transduction

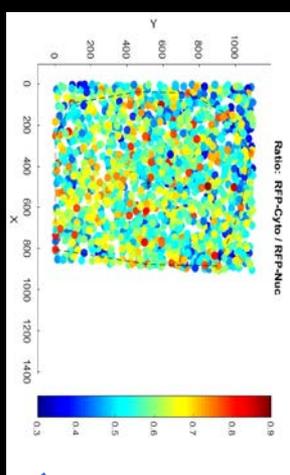
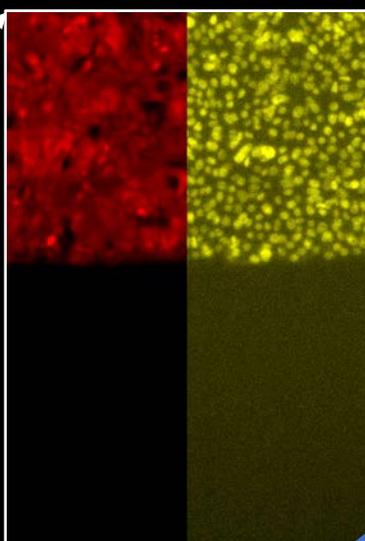


Sebastian
Losert Lab



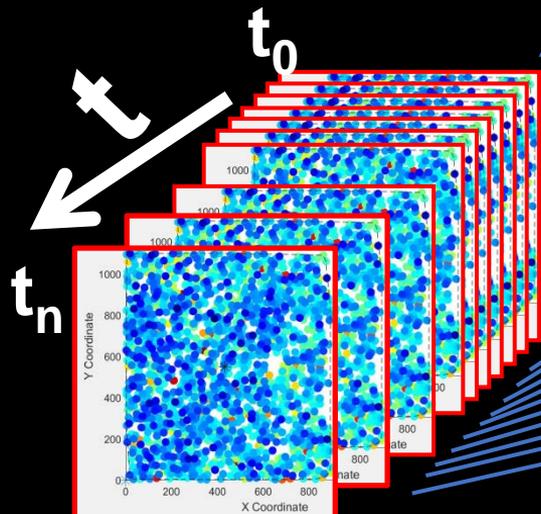
Nuclear - mVenus

ERK activation Cf/Nf of ERKTR-mCherry

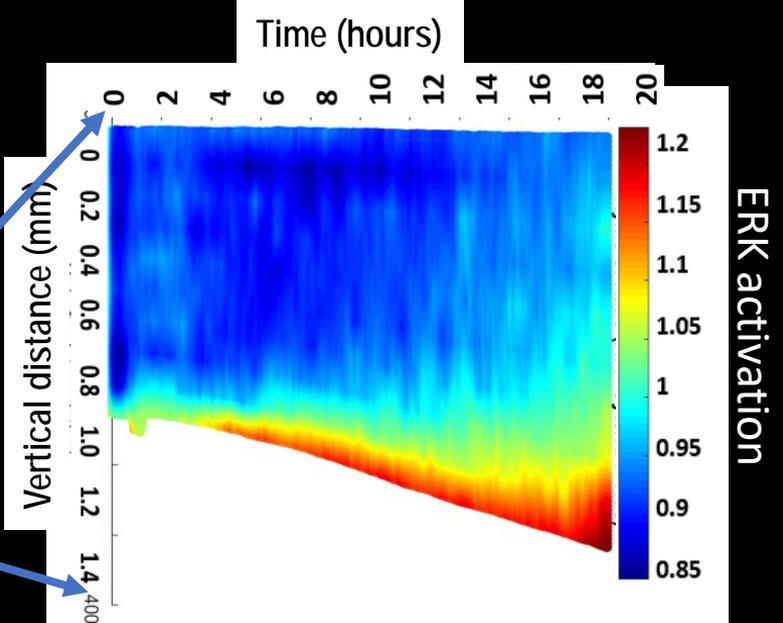
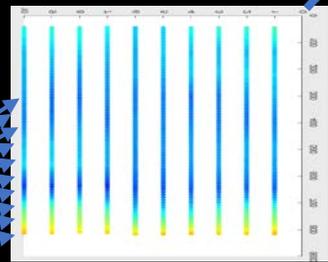


Kymograph

- ERK activation
- migration direction
- migration speed



Average in horizontal axis



ERK activation

Electrically regulated STEN- CON paradigm in collective cell migration.

1. Epithelial cells show similar response

CON – cytoskeletal oscillation (membrane)

STEN - signaling induced large protrusion.

**2. Cell sheets respond to EF by collective directional migration, showing “wave propagation” in migration directionality and speed “CON” and “STEN”.
(Losert group)**

3. Probing into the intracellular signaling pathways

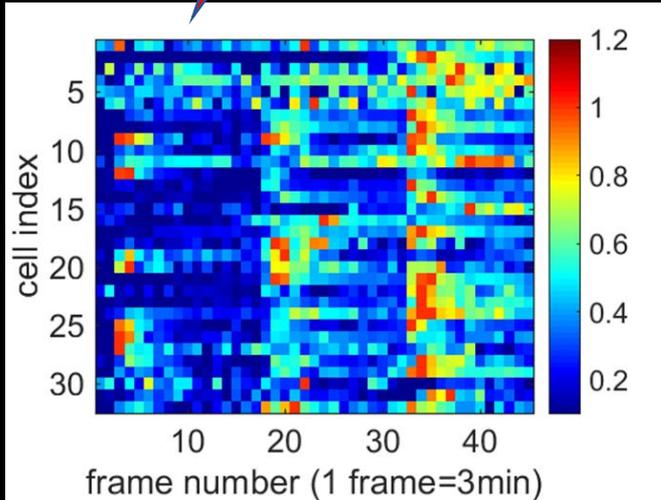
(with ASU; MDU; JHU; John Albeck lab, UC Davis)

4. Collective sensing and responding – electrotaxis and chemotaxis (Mayor lab)

5. Collective cell migration in vivo (Chuong lab USC)

Current direction 1

To electrically control ERK activation



Amplitude modulation (AM)
Frequency modulation (FM)



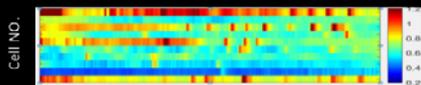
- Cell migration
- Cell survival/proliferation
- Apoptosis
- Cell-cycle regulation
- ...

Current direction 2

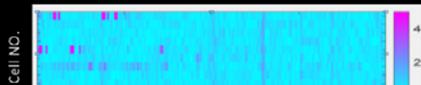
New Paradigms -- STEN \longleftrightarrow CON in collective migration

Single cell paradigms

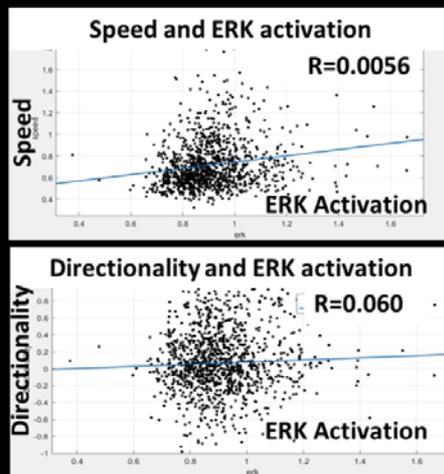
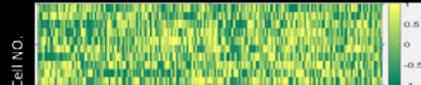
ERK Activation of individual cell



Speed of individual cell



Directionality of individual cell

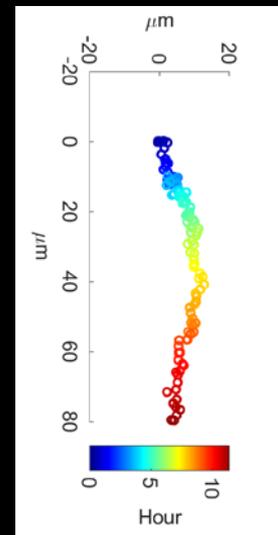


Losert, MDU; Devreotes, JHU

Multi-cell paradigms



+ EF 4V/cm
↓
-



Movement of the cell sheet

Thank you!

