

Electrical, Chemical & Mechanical Excitable Networks in

# Collective Cell Migration



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**“...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**



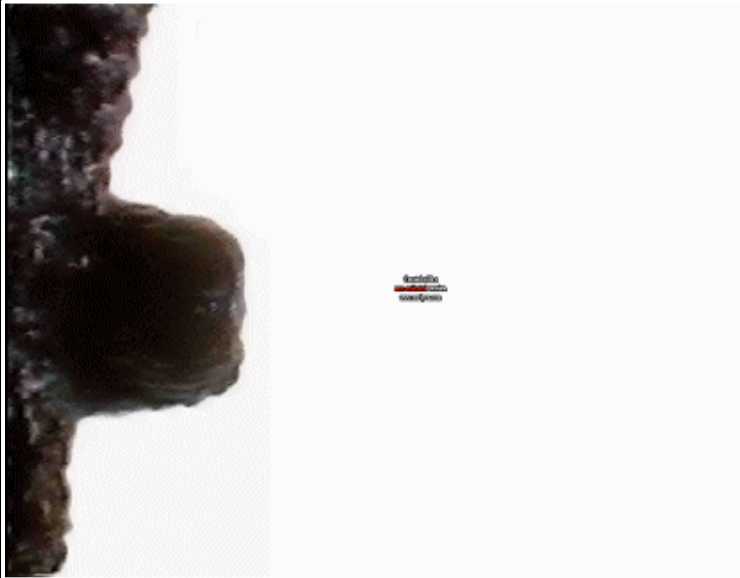
The Management of Combat Wounds: The British Military Experience. ADV. WOUND CARE, 2016, 5(10).



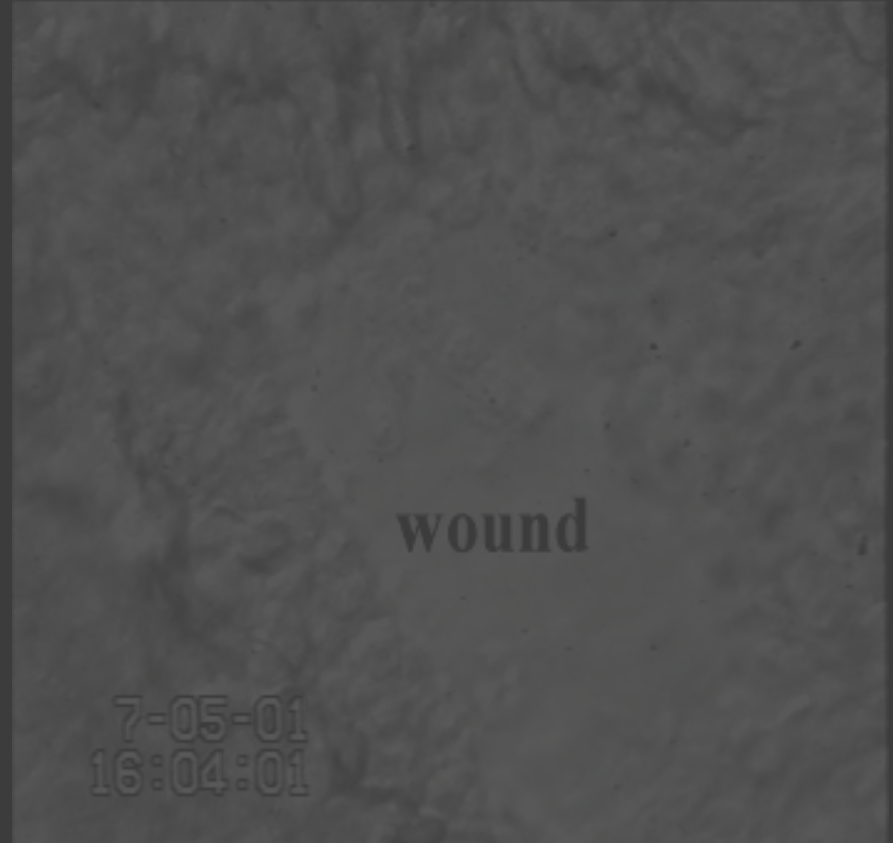
[https://en.wikipedia.org/wiki/Battlefield\\_medicine](https://en.wikipedia.org/wiki/Battlefield_medicine)

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

# Regeneration



100μm



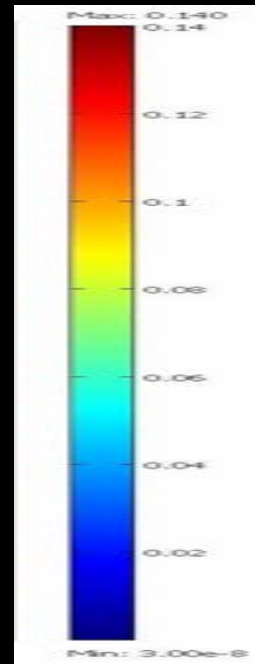
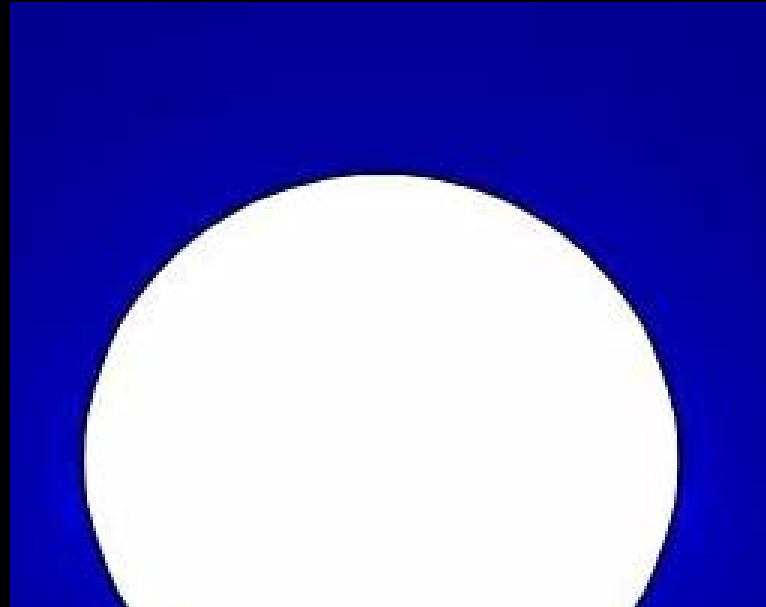
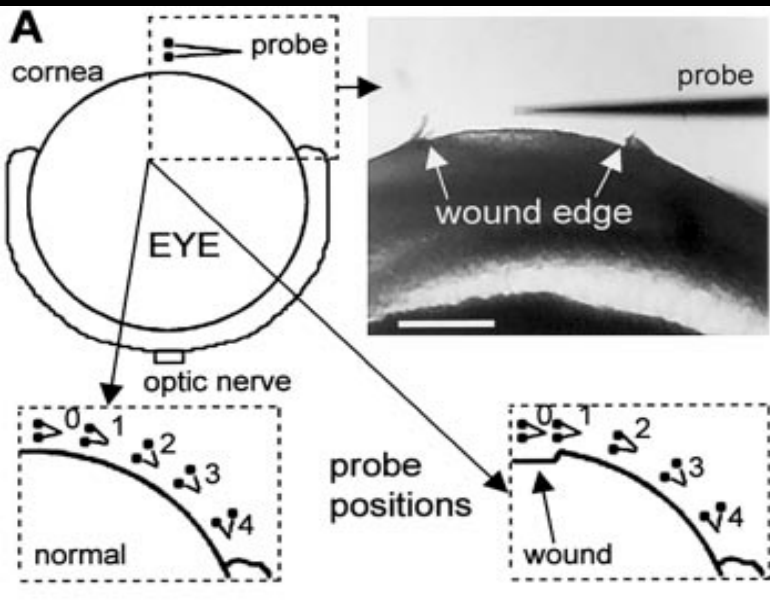
# Excitable Networks

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

**Electrical**

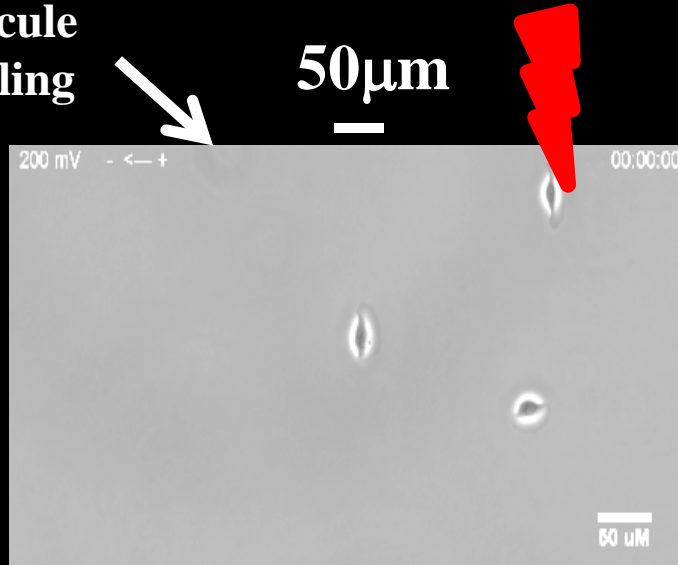
– wound itself naturally produce electric fields

**Mechanical:** stiffness and tension



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

Molecule  
signaling



*Electric field*

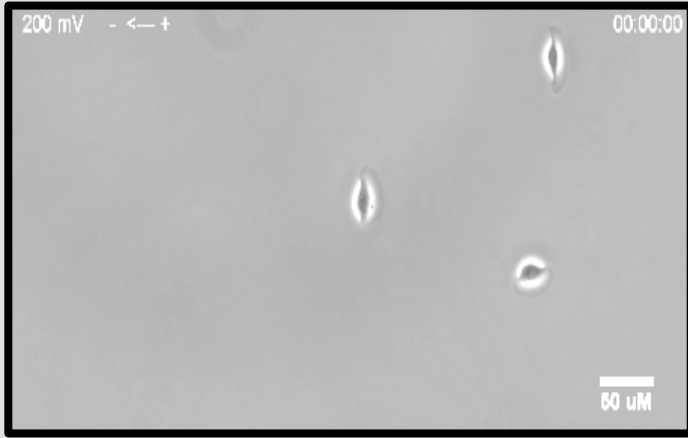
*determines whether wounds close or open up.*



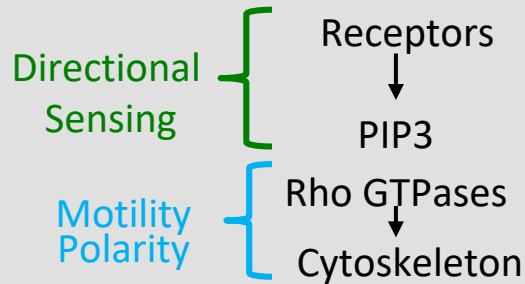
Significantly scaling up in size and time

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

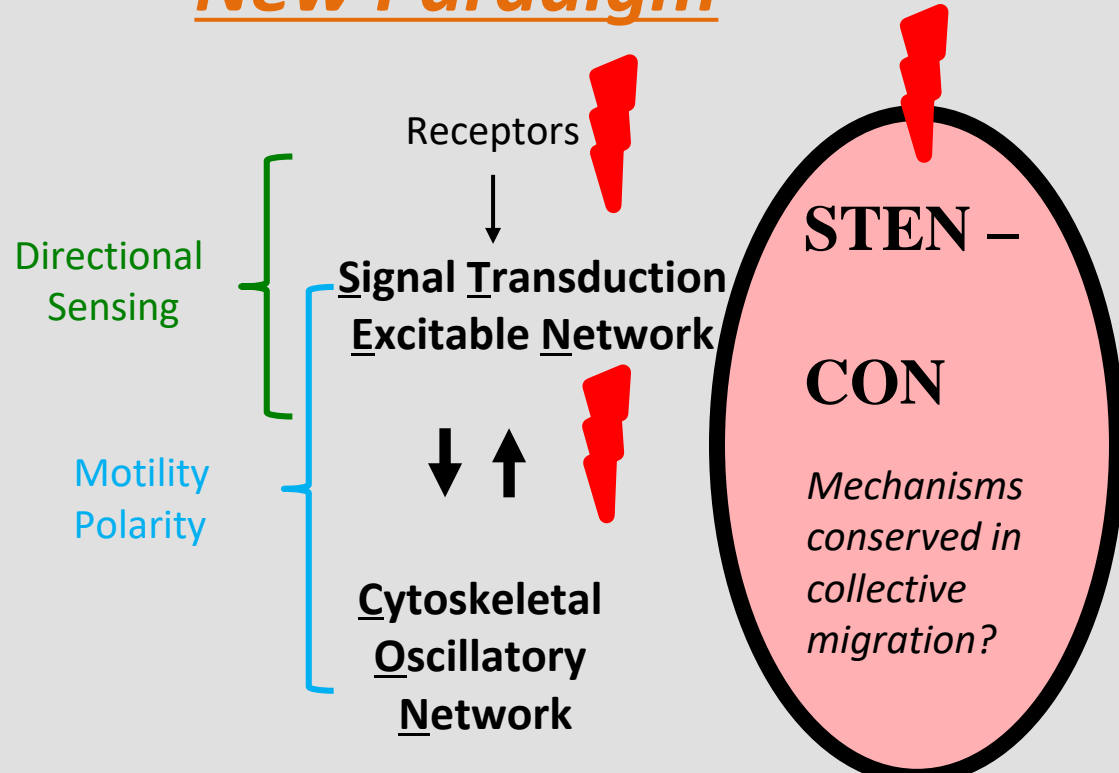


## 1998 Paradigm



*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

Dr. Yan  
Zhang

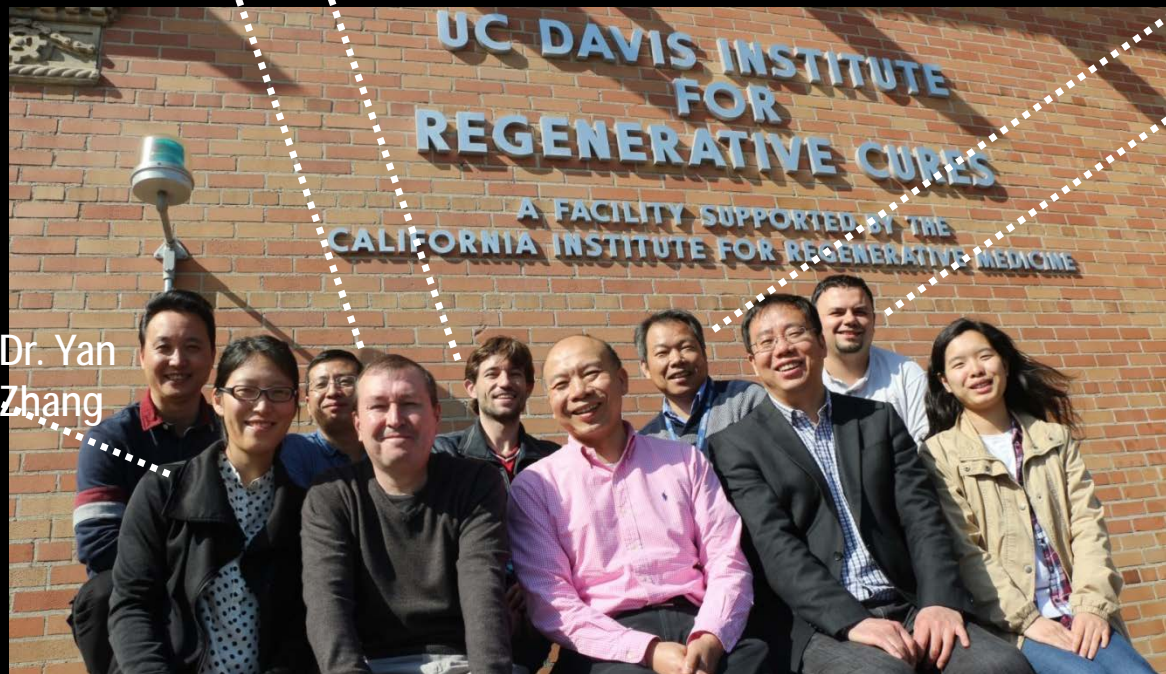


Kan Zhu



Liang Guo

**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

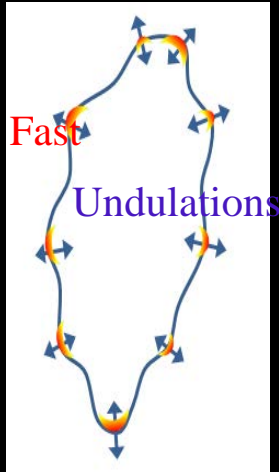
*CON – cytoskeletal oscillation (membrane)*

*STEN - signaling induced large protrusion*

*(with Alex Mogilner, NYU)*

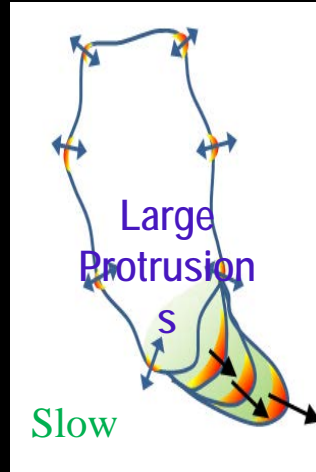
CON

(Cytoskeletal  
Oscillatory Network)



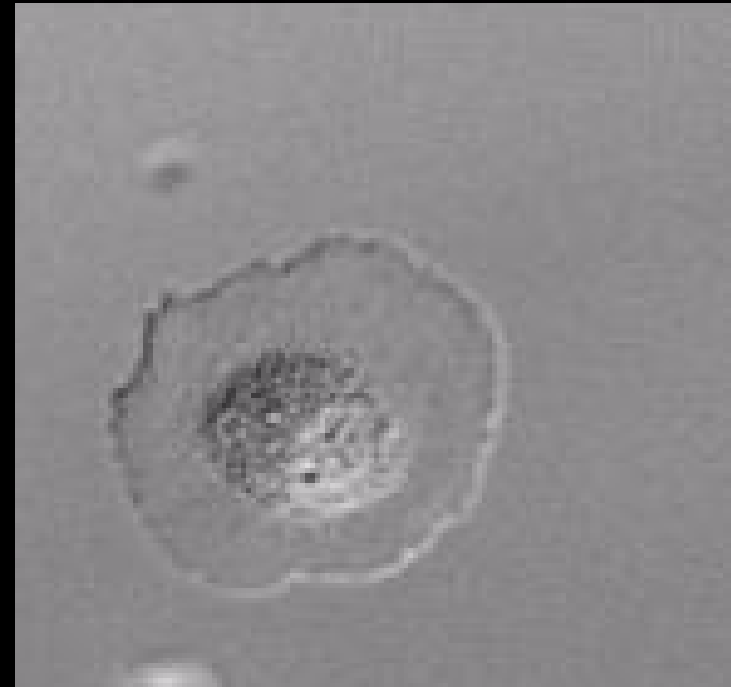
STEN

(Signal Transduction  
Excitable Network)

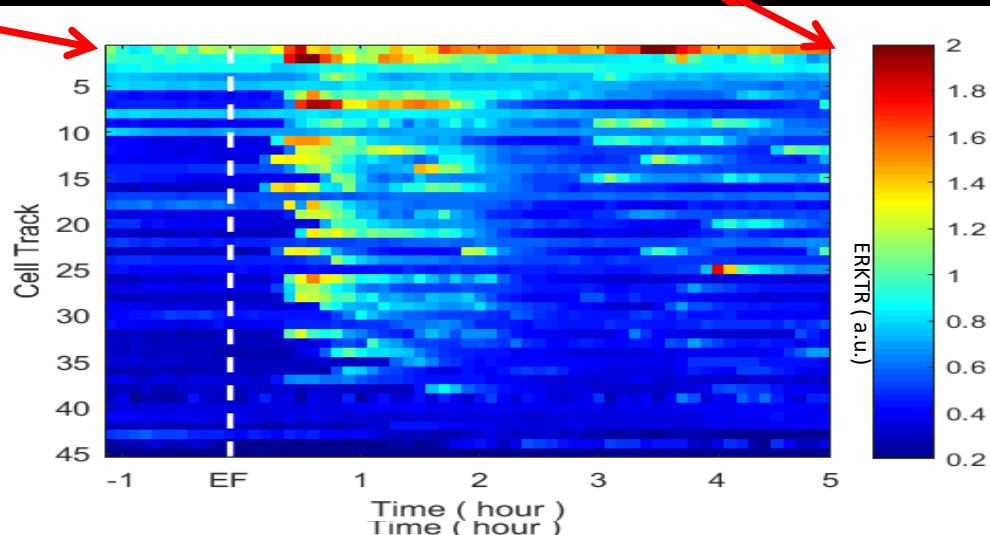
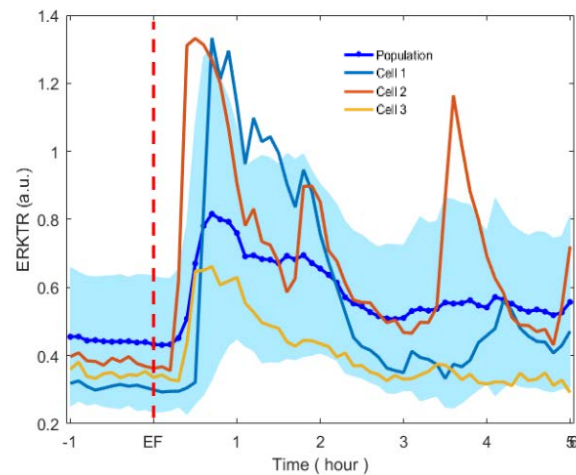
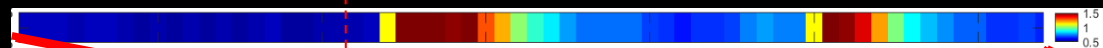
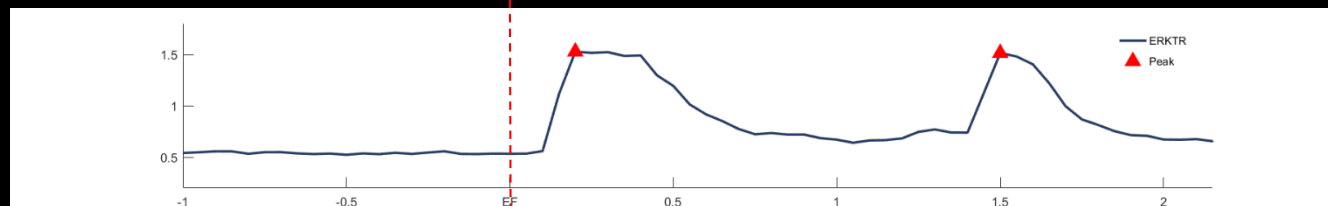
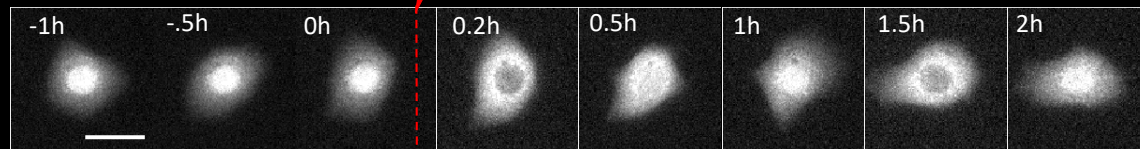


20  $\mu\text{m}$

00:00

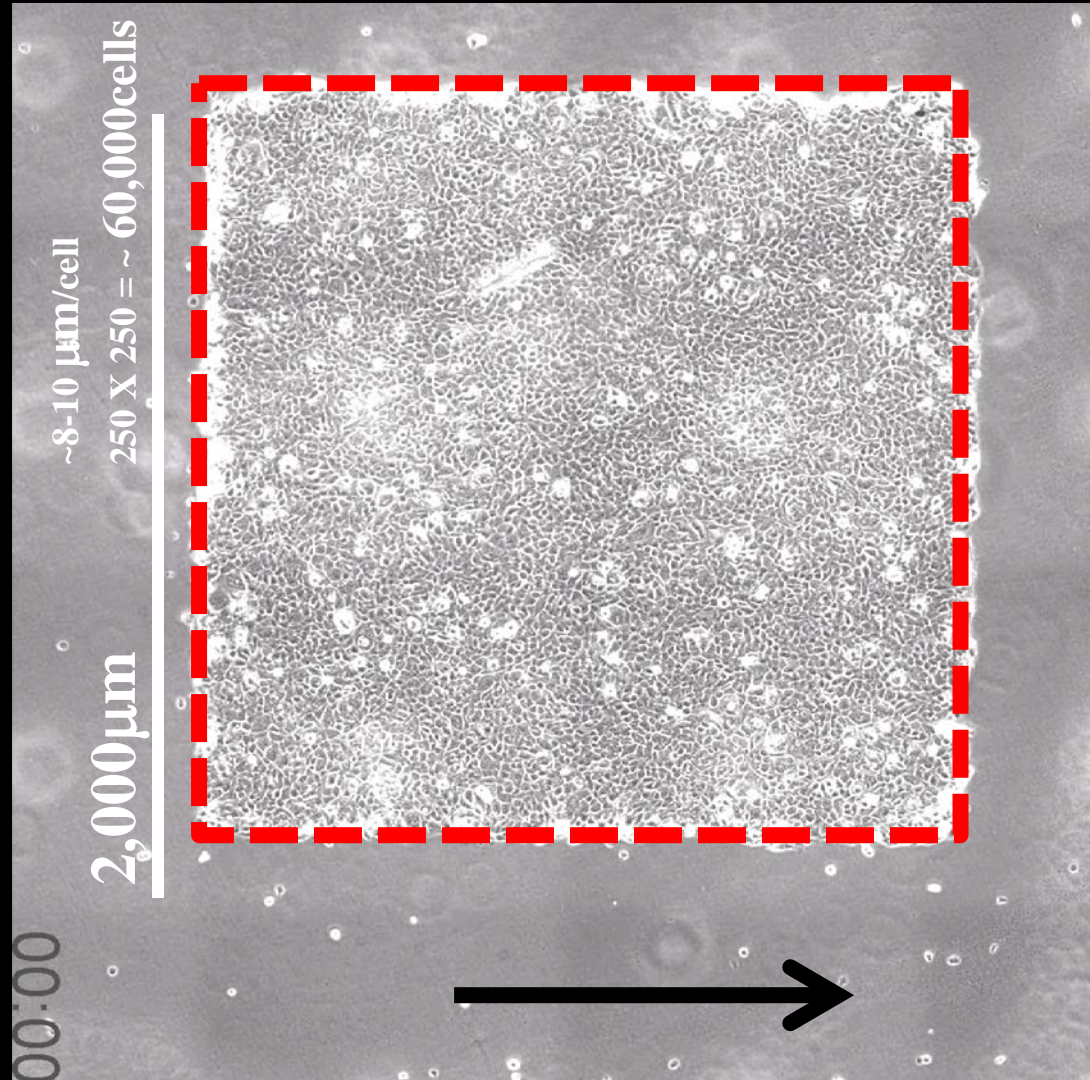


# DC electric fields activate ERK



**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

Receptors  
↓  
Excitatory Network  
↑  
Cytoskeletal  
Oscillatory  
Network

STEN - CON

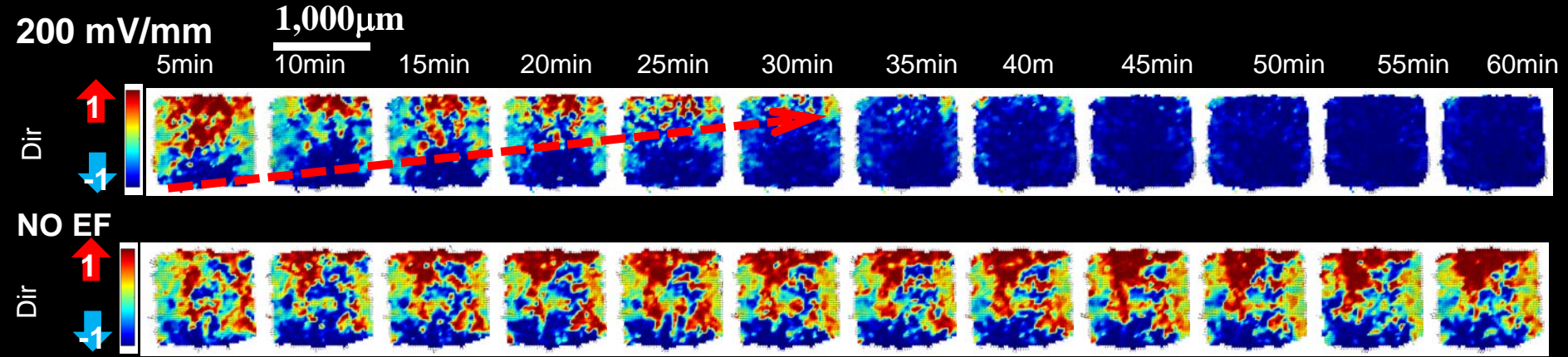
Mechanism  
possibly conserved  
in collective  
migration?

 Quantitative  
analysis of  
Migration

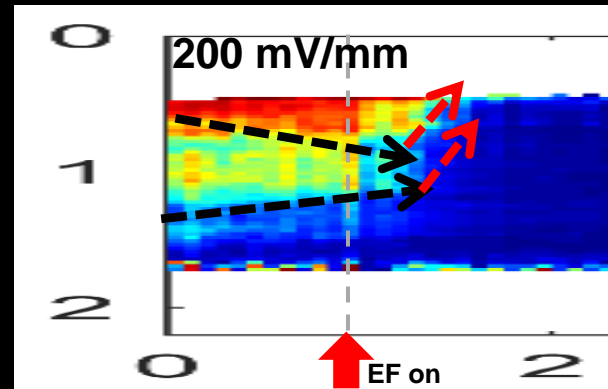
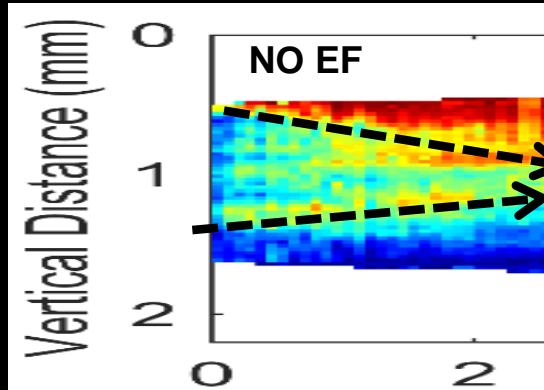
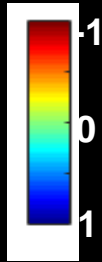
Cytoskeletal  
dynamics

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



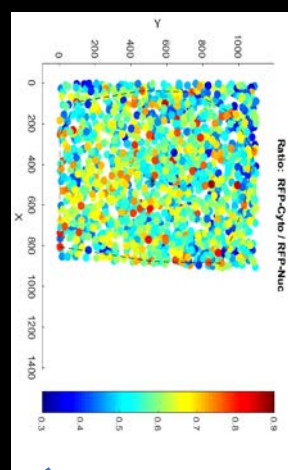
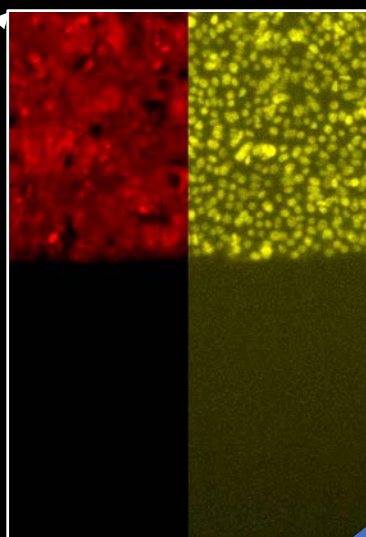
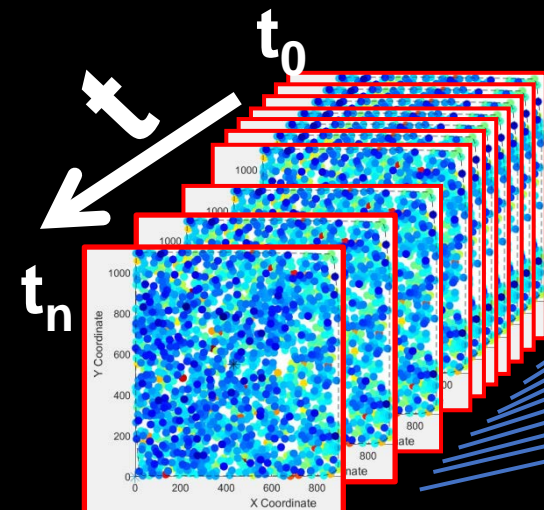
Signaling  
Transduction

Sebastian  
Losert Lab

STEN - CON

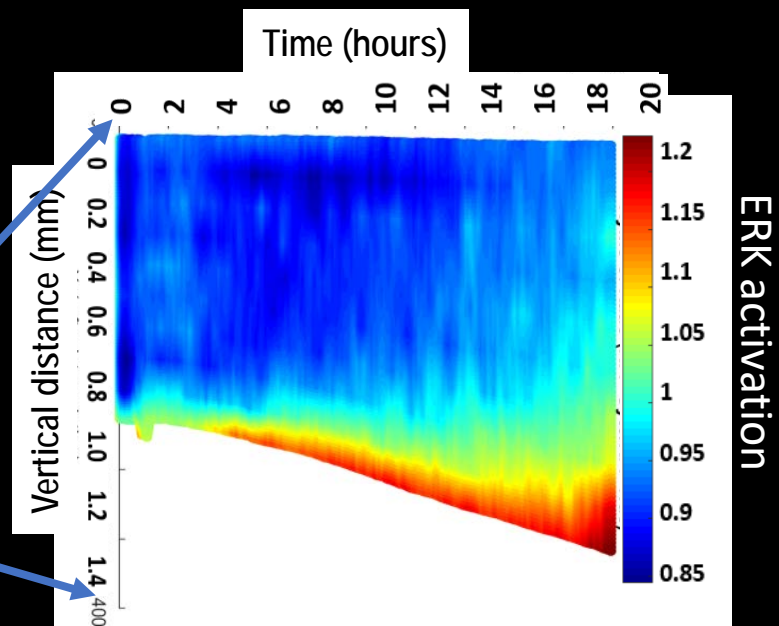
Nuclear - mVenus

ERK activation Cf/Nf  
of ERKTR-mCherry

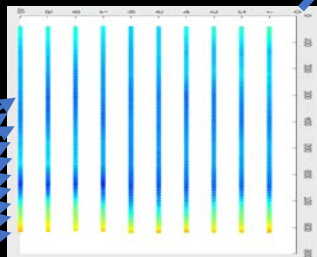


Kymograph

- ERK activation
- migration direction
- migration speed



Average in  
horizontal axis



## **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)**

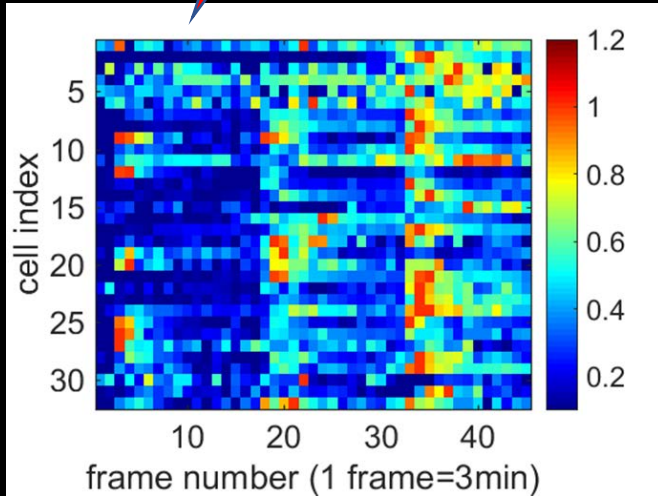
### **3. Probing into the intracellular signaling pathways (with ASU; MDU; JHU; John Albeck lab, UC Davis)**

### **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



Amplitued modulation (AM)  
Frequency modulation (FM)



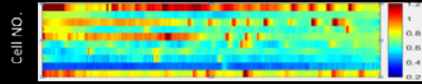
- Cell migration
- Cell survival/proliferation
- Apoptosis
- Cell-cycle regulation
- ...

# Current direction 2

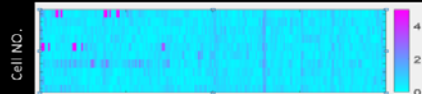
*New Paradigms -- STEN  $\longleftrightarrow$  CON in collective migration*

## Single cell paradigms

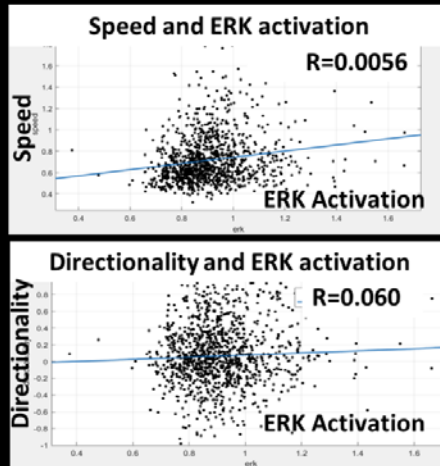
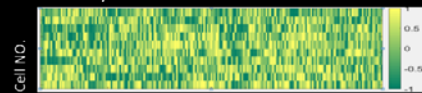
ERK Activation of individual cell



Speed of individual cell

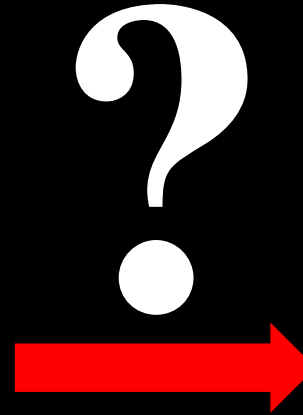


Directionality of individual cell

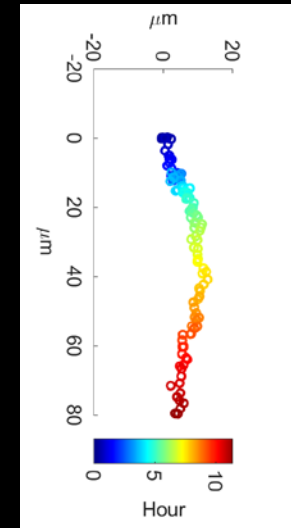


*Losert, MDU; Devreotes, JHU*

## Multi-cell paradigms



+ EF 4V/cm  
↓  
-



Movement of the cell sheet

*Thank you!* 