REPORT DOCUMENTATION PAGE

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01-02-2022	Final Report	30-Sep-2017 - 29-Sep-2021

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Final Report: Predicting Tissue Dynamics based on Stochastic Variations in Cell Stiffness and Spatial Clustering within the Tissue Environment

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5c. PROGRAM ELEMENT NUMBER
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San Diego State University Foundation
5250 Campanile Drive

San Diego, CA 92182 -1931

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The views, opinions and/or findings contained in this report are those of the author(s) and should not contrued as an official Department of the Army position, policy or decision, unless so designated by other documentation.

14. ABSTRACT

15. SUBJECT TERMS

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a. REPORT	b. ABSTRACT	c. THIS PAGE			Parag Katira
UU	UU	UU	UU		19b. TELEPHONE NUMBER 619-594-2032

RPPR Final Report
as of 24-Feb-2022

Agency Code: 21XD

Proposal Number: 71534MA **Agreement Number: W911NF-17-1-0413**
INVESTIGATOR(S):

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Country: USA
DUNS Number: 073371346 EIN: 956042721
Report Date: 29-Dec-2021 Date Received: 01-Feb-2022
Final Report for Period Beginning 30-Sep-2017 and Ending 29-Sep-2021
Title: Predicting Tissue Dynamics based on Stochastic Variations in Cell Stiffness and Spatial Clustering within the Tissue Environment
Begin Performance Period: 30-Sep-2017 **End Performance Period:** 29-Sep-2021
Report Term: 0-Other
Submitted By: Parag Katira Email: pkatira@mail.sdsu.edu
Phone: (619) 594-2032
Distribution Statement: 1-Approved for public release; distribution is unlimited.

STEM Degrees: 7 **STEM Participants:** 12

Major Goals: The main goal of this project was to understand the role of local and global heterogeneity in the mechanical properties of cells within a tissue on overall tissue dynamics. To achieve this goal, the work to be performed was split to focus on the following main aims -

1) Determine the mobility of cells within the tissue environment as a function of the mechanical properties of the cell and its neighbors

Cells within dense tissue environments can migrate by exchanging spaces with neighbors and generating traction forces on the surrounding extra-cellular matrix. The cells can move individually or in clusters depending on the mechanical interactions between each other and their environment. As the tumor micro-environment is extremely heterogeneous in its architecture and mechanical properties, how this heterogeneity influences single and collective cell migration is extremely important to predict overall tissue dynamics.

2) Determine the rate of clustering and spatial segregation of cells with similar mechanical properties within the tissue environment

As cell migrate through a tissue environment, they can exchange neighbors and segregate themselves from certain cell types while aggregate with certain others giving rise to distinct distributions of cell populations within the tissue environment. How cells with different mechanical phenotypes interact with each other and form patterns within the tissue environment is investigated as a part of this aim.

3) Determine the likelihood of tumor-like malignant cell populations, identified by their peculiar mechanical properties, growing and forming malignant tumors within these tissue environments.

With a specific focus on tumor formation within healthy tissue environments, we aimed to predict how the mechanical heterogeneity of a tissue environment gives rise to cell clustering, proliferation and invasion of one specific phenotype. Such a process would shed light on the initiation and growth of malignant tumors in healthy tissue environments.

Accomplishments: Aim 1: Determine the mobility of cells within the tissue environment as a function of the mechanical properties of the cell and its neighbors.

Mobility within a three-dimensional (3D) matrix environment can be characterized by the average velocity of cell migration and the persistence length of the path it follows. Computational models that aim to predict cell migration within such 3D environments need to be able predict both properties as a function of the various cellular and extra-cellular factors that influence the migration process. We developed a new stochastic algorithm that can simulate and analyze 3D cell migration occurring over days with a computation time of minutes, opening new possibilities of testing and predicting long-term cell migration behavior as a function of a large variety of cell and matrix properties. In this model, the matrix elements are generated as needed and stochastically based on the biophysical and biochemical properties of the ECM the cell migrates through. This approach significantly reduces the computational resources required to track and calculate cell matrix interactions. Using this algorithm, we predict the effect of various cellular and matrix properties such as cell polarity, cell mechanoactivity, matrix fiber density, matrix stiffness, fiber alignment, and fiber binding site density on path persistence of cellular migration and the mean squared displacement of cells over long periods of time. The detailed model description and applications can be found in the publication - A stochastic algorithm for accurately predicting path persistence of cells migrating in 3D matrix environments by B. Yeoman and P. Katira, PLOS One, 13(11): e0207216 (2018)

Next, using this new modeling approach, we worked to understand how various environmental and cellular factors influence small clusters of cells migrating collectively within a 3D fibrous matrix. We combined existing knowledge of single-cell migration in 2D and 3D environments, prior experimental observations of cell–cell interactions and collective migration, and above-described stochastic model of cell migration in 3D matrices, to simulate the migration of cell clusters in different physiologically relevant environments. Our results showed that based on the extracellular environment and the strength of cell–cell mechanical coupling, two distinct optimal approaches to driving collective cell migration emerge (see figure 1 in the attached document). The ability to effectively employ these two distinct migration strategies might be critical for cells to collectively migrate through the heterogeneous tissue environments within the body. The results and their implications are described in detail in the publication - To Lead or to Herd: Optimal strategies for collective cell migration in heterogenous 3D environments by T. Collins, B. M. Yeoman and P. Katira, Biomechanics and Modeling in Mechanobiology, 19, pages1551–1564 (2020)

Aim 2: Determine the rate of clustering and spatial segregation of cells with similar mechanical properties within the tissue environment

In collaboration with experimentalists from the University of Leipzig, we studied the mixing and demixing behavior of mechanically heterogeneous cell populations in 2D environments. The results of the experiments did not fit with any of the existing theories such as the Differential Adhesion Hypothesis (DAH), or a differential interfacial tension (DIT) model, or rigidity percolation and jamming hypothesis and so on. Instead, we found that there are a number of other mechanisms that could be involved including but not limited to - 1) extensile vs contractile behavior of cellular networks in response to differential cell-substrate interactions, 2) motility pattern differences leading to fluid-like separation between turbulent and laminar regimes, 3) formation of supracellular structures such as actin-myosin cables spanning multiple cells and 4) rearrangements and forces arising from cellular death and division. By taking a deeper look at the effect of cellular death and division on tissue rearrangements, we found that just the occurrence of death and division effects can drive symmetry breaking and segregation within tissues containing cells with different mechanical properties. Additionally, depending on the forces that drive cell death and division, this can lead to different degrees of segregation and self-organization within the tissue (see figure 2 of the attached document). Our experimental observations, modeling advancements and results are described in detail in the publication - Anomalous cell sorting behavior in mixed monolayers discloses hidden system complexities by Paul Heine, Jürgen Lippoldt, Gudur Ashrith Reddy, Parag Katira, Josef A. Käs. New Journal of Physics, 23(4), 043034 (2021).

Along similar lines, we investigated cellular organization along patterned surfaces with soft and stiff regions. We found that while most cells migrated towards stiffer regions, some highly metastatic cells did not show this trend and instead showed equal preference for either region. We also found that the cells that showed this behavior were less sticky compared to the other cells, stiffer, and more contractile. Using our computational model, we showed that these differences in mechanical properties were associated with an increased actin-myosin force generation. The computational model accurately recreated the cell organization phenomena observed experimentally on soft and stiff regions for a heterogeneous population of cells (see figure 3 in the attached document). The experimental work was done in our collaborator’s lab at UC San Diego. The experimental and computational modeling details are described in the publication - Adhesion Strength and Contractility Enable Metastatic Cells to become Adurotactic by Benjamin Yeoman, Gabriel Shatkin, Pranjali Beri, Parag Katira, Adam J Engler, Cell Reports, 34(10), 108816 (2021).

Aim 3: Determine the likelihood of tumor-like malignant cell populations, identified by their peculiar mechanical properties, growing, and forming malignant tumors within these tissue environments.

We used our mechanics-based in-silico models of cell-cell interactions and cell population dynamics within 3D environments to probe how heterogeneity in cell mechanics drives tissue and tumor dynamics. Our simulations showed that the initial heterogeneity in the mechanical properties of individual cells and the arrangement of these heterogenous sub-populations within the environment can dictate overall cell population dynamics and a shift towards the growth of malignant cell phenotypes within healthy tissue environments. The overall heterogeneity in the cellular mechanotype and their spatial distributions can be quantified by a single “patchiness” index, which is the ratio of the global to local heterogeneity in cell populations. We observe that there exists a threshold patchiness index beyond which an overall healthy cell population of cells will show a steady shift towards a more malignant phenotype (see figure 4 in the attached document). Based on these results we suggest that the “patchiness” of a tumor or tissue sample, can be an early indicator for malignant transformation and cancer occurrence in benign tumors or healthy tissues. Additionally, we believe that tissue patchiness, measured either by biochemical or biophysical markers, can become an important metric in predicting tissue health and disease likelihood just as landscape patchiness is an important metric in ecology. These results are described in a manuscript currently under review.

Training Opportunities: Three Doctoral Students were trained on research related to this project -

1) Benjamin Yeoman
2) Gudur Ashrith Reddy
3) Esra Tiftik (female)

Three Master's Thesis Students were trained on research related to this project -

1) Zibah Mirzakhel (female)
2) Tyler Collins
3) Eduardo Zepeda (Hispanic)

Six Undergraduate Students were trained on research related to this project -
1) Briana Manns (female)
2) Savannah Ter Veer (female)
3) Jennifer Boman (female)
4) Jhovanna Garcia (female, Hispanic)
5) Ivette Silva (female, Hispanic)
6) Mustafa Haleem

One High School student was trained on research related to this project -
1) Kate Spencer (female)

RPPR Final Report
as of 24-Feb-2022

Results Dissemination: The work conducted under this award was published in 6 peer-reviewed publications:

1. Anomalous cell sorting behavior in mixed monolayers discloses hidden system complexities
Paul Heine, Jürgen Lippoldt, Gudur Ashrith Reddy, Parag Katira, Josef A. Käs. New Journal of Physics, 23(4), 043034 (2021)

2. Adhesion Strength and Contractility Enable Metastatic Cells to become Adurotactic
Benjamin Yeoman, Gabriel Shatkin, Pranjali Beri, Parag Katira, Adam J Engler, Cell Reports, 34(10), 108816 (2021)

3. Computational Models of Migration Modes Improve our Understanding of Metastasis
Gabriel Shatkin, Benjamin Yeoman, Katherine Birmingham, Parag Katira, Adam J Engler, APL Bioengineering, 4 (4), 041505 (2020)
Featured on the journal cover page.

4. To Lead or to Herd: Optimal strategies for collective cell migration in heterogenous 3D environments
T. Collins, B.M. Yeoman and P. Katira, Biomechanics and Modeling in Mechanobiology, 19, pages1551–1564 (2020)

5. Cell adhesiveness serves as a biophysical marker for metastatic potential
P. Beri, A. Popravko, B. Yeoman, A. Kumar, K. Chen, E. Hodzic, A. Chiang, A. Banisadr, J.K. Placone, H. Carter, S.I. Fraley, P. Katira and A.J. Engler; Cancer Research, 80 (4), 901-911 (2020)

6. A stochastic algorithm for accurately predicting path persistence of cells migrating in 3D matrix environments
B. Yeoman and P. Katira, PLOS One 13(11): e0207216 (2018)

One more manuscript is currently under review.

The work was also presented in various conferences and symposia as either a poster or oral presentation -

1. Cell Mechanotype Dictates Rigidity Sensing and Enables Metastatic Cells to Become Adurotactic
B. Yeoman*, G. Shatkin, P. Beri, A. J. Engler, P. Katira, Oral Presentation at the 2020 BMES Meeting, Virtual (Oct 2020)

2. Cell Mechanotype Dictates Rigidity-Sensing And Enables Metastatic Cells To Become Adurotactic
B. Yeoman*, G. Shatkin, P. Beri, A. J. Engler, P. Katira, Oral Presentation at the 2020 SB3C Meeting, Virtual (June 2020)

3. Modeling Co-Evolution of Mechanically Heterogeneous Cell Populations
G.A. Reddy* and P. Katira, Poster Presentation at the 2020 Biophysical Society Meeting, San Diego (Feb 2020)

4. To Lead or to Herd: Optimal Strategies for Collective Cell Migration in Heterogeneous Tissue Environments
T. Collins*, B. Yeoman and P. Katira, Oral Presentation at the 2019 BMES Meeting, Philadelphia, PA (Oct 2019)

5. Anomalous mixing and demixing behavior of cell population in confluent monolayers
G. A. Reddy* and P. Katira, Poster Presentation at the 10th Symposium on the Physics of Cancer, Leipzig, Germany (Sept 2019)

6 Optimal Strategies for individual and collective cell migration during cancer metastasis
B. Yeoman, T. Collins, P. Beri, A.J. Engler, P. Katira*, Oral Presentation at the 10th Symposium on the Physics of Cancer, Leipzig, Germany (Sept 2019)

7. Can intra-tumor heterogeneity in cell mechanotype predict benign to malignant transformations in tumors
Z. Mirzakhel, J. Boman, B. Manns, S. Van Teer and P. Katira*, Poster Presentation at the Gordon Research Conference on Physical Sciences in Oncology, Galveston, TX (Feb 2019)

8. Adhesion Strength Regulates Metastatic Tumor Cell Durotaxis
B. Yeoman*, P. Beri, A.J. Engler and P. Katira, Poster Presentation at the 2018 BMES Meeting, Atlanta, GA (Oct'

2018)

9. Predicting Tumor Malignancy based on Stochastic Variations in Cell Stiffness and Spatial Clustering within Tissue Environments
Z. Mirzakhel, J. Boman, B. Manns, S. Van Teer and P. Katira*, Oral Presentation at the 2018 APS March Meeting, Los Angeles, CA (May' 2018)

Honors and Awards: PI Katira was awarded the Outstanding Leadership in Engineering Award from the San Diego County Engineering Council (2021)

Graduate Student, Benjamin Yeoman, Ph.D. candidate in Bioengineering received NSF - SDSU S-STEM Fellowship (2018)

Graduate Student, Benjamin Yeoman, Ph.D. candidate in Bioengineering received NCI T32 training grant (2021)

Undergraduate Student, Jhovanna Garcia was selected for the Department of Energy's (DOE) Science Undergraduate Laboratory Internships (SULI) program internship (2021)

Protocol Activity Status:

Technology Transfer: Nothing to Report

PARTICIPANTS:

Participant Type: PD/PI
Participant: Parag Katira
Person Months Worked: 2.00 **Funding Support:**
Project Contribution:
National Academy Member: N

Participant Type: Graduate Student (research assistant)
Participant: Benjamin Yeoman
Person Months Worked: 3.00 **Funding Support:**
Project Contribution:
National Academy Member: N

Participant Type: Graduate Student (research assistant)
Participant: Gudur Ashrith Reddy
Person Months Worked: 6.00 **Funding Support:**
Project Contribution:
National Academy Member: N

Participant Type: Graduate Student (research assistant)
Participant: Esra Tiftik
Person Months Worked: 3.00 **Funding Support:**
Project Contribution:
National Academy Member: N

Participant Type: Graduate Student (research assistant)

Participant: Zibah Mirzakhel
Person Months Worked: 6.00 **Funding Support:**
Project Contribution:
National Academy Member: N

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Participant: Tyler Collins
Person Months Worked: 3.00 **Funding Support:**
Project Contribution:
National Academy Member: N

Participant Type: Graduate Student (research assistant)
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Person Months Worked: 3.00 **Funding Support:**
Project Contribution:
National Academy Member: N

Participant Type: Undergraduate Student
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Person Months Worked: 1.00 **Funding Support:**
Project Contribution:
National Academy Member: N

Participant Type: Undergraduate Student
Participant: Savannah Ter Veer
Person Months Worked: 1.00 **Funding Support:**
Project Contribution:
National Academy Member: N

Participant Type: Undergraduate Student
Participant: Jennifer Boman
Person Months Worked: 1.00 **Funding Support:**
Project Contribution:
National Academy Member: N

Participant Type: Undergraduate Student
Participant: Jhovanna Garcia
Person Months Worked: 1.00 **Funding Support:**
Project Contribution:
National Academy Member: N

Participant Type: Undergraduate Student
Participant: Ivette Silva
Person Months Worked: 1.00 **Funding Support:**

Project Contribution:
National Academy Member: N

Participant Type: Undergraduate Student
Participant: Mustafa Haleem
Person Months Worked: 1.00 **Funding Support:**
Project Contribution:
National Academy Member: N

Participant Type: High School Student
Participant: Kate Spencer
Person Months Worked: 1.00 **Funding Support:**
Project Contribution:
National Academy Member: N

ARTICLES:

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Journal: PLOS ONE
Publication Identifier Type: DOI Publication Identifier: 10.1371/journal.pone.0207216
Volume: 13 Issue: 11 First Page #:
Date Submitted: 8/15/19 12:00AM Date Published: 11/1/18 7:00AM
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Article Title: A stochastic algorithm for accurately predicting path persistence of cells migrating in 3D matrix environments
Authors: Benjamin Michael Yeoman, Parag Katira, Wenguo Cui
Keywords: Cell Migration, Computational Biology, Stochastic Modeling
Abstract: The manuscript describes a novel computational algorithm to compute cell-3D matrix interactions at the individual fiber level to predict cell migration through such environments. The algorithm significantly lowers calculation time while maintaining a high degree of detail regarding the mechanics of these interactions, cell shape and the architecture of the 3D environment. Using this approach we can simulate the migration of cells through different 3D matrix environments occurring over days within a matter of seconds, allowing us to make accurate predictions regarding cell mobility and persistence as a function of the various cellular and extra-cellular properties. These simulations are extremely useful in prediction of biological processes such as wound healing, immune response and cancer metastasis.
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Journal: MRS Bulletin
Publication Identifier Type: DOI Publication Identifier: 10.1557/mrs.2019.19
Volume: 44 Issue: 2 First Page #: 113
Date Submitted: 8/15/19 12:00AM Date Published: 2/1/19 8:00AM
Publication Location:
Article Title: Molecular motors in materials science
Authors: Henry Hess, Parag Katira, Ingmar H. Riedel-Kruse, Stanislav Tsitkov
Keywords: Active Matter, Material Mechanics, Molecular Motors, Synthetic Biology
Abstract: Materials can be endowed with unique properties by the integration of molecular motors. Molecular motors can have a biological origin or can be chemically synthesized and produce work from chemical energy or light. Their ability to access large internal or external reservoirs of energy enables a wide range of nonequilibrium behaviors, including the production of force, changes in shape, internal reorganization, and dynamic changes in mechanical properties—muscle tissue is one illustration of the possibilities. Current research efforts advance our experimental capabilities to create such “active matter” by using either biomolecular or synthetic motors, and also advance our theoretical understanding of these materials systems. Here, we introduce this exciting research field and highlight a few of the recent advances as well as open questions.
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Volume: Issue: First Page #:
Date Submitted: 7/30/20 12:00AM Date Published: 1/29/20 4:00PM
Publication Location:
Article Title: To lead or to herd - optimal strategies for 3D collective migration of cell clusters
Authors: Tyler A. Collins, Benjamin M. Yeoman & Parag Katira
Keywords: Cell migration, tissue dynamics, cell clusters
Abstract: Cells migrating in clusters play a significant role in a number of biological processes such as embryogenesis, wound healing, and tumor metastasis during cancer progression. A variety of environmental and biochemical factors can influence the collective migration of cells with differing degrees of cell autonomy and inter-cellular coupling strength. For example, weakly coupled cells can move collectively under the influence of contact guidance from neighboring cells or the environment. Alternatively strongly coupled cells might follow one or more leader cells to move as a single cohesive unit. Additionally, chemical and mechanical signaling between these cells may alter the degree of coupling and determine effective cluster sizes. Being able to understand this collective cell migration process is critical in the prediction and manipulation of outcomes of key biological processes. Here we focus on understanding how various environmental and cellular factors influence small clusters of...
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Journal: Cancer Research
Publication Identifier Type: DOI Publication Identifier: 10.1158/0008-5472.CAN-19-1794
Volume: 80 Issue: 4 First Page #: 901
Date Submitted: 8/1/20 12:00AM Date Published: 2/1/20 8:00AM
Publication Location:
Article Title: Cell Adhesiveness Serves as a Biophysical Marker for Metastatic Potential
Authors: Pranjali Beri, Anna Popravko, Benjamin Yeoman, Aditya Kumar, Kevin Chen, Enio Hodzic, Alyssa Chiar
Keywords: Cell mechanics, Cancer, Heterogeneity
Abstract: Tumors are heterogeneous and composed of cells with different dissemination abilities. Despite significant effort, there is no universal biological marker that serves as a metric for metastatic potential of solid tumors. Common to disseminating cells from such tumors, however, is the need to modulate their adhesion as they detach from the tumor and migrate through stroma to intravasate. Adhesion strength is heterogeneous even among cancer cells within a given population, and using a parallel plate flow chamber, we separated and sorted these populations into weakly and strongly adherent groups; when cultured under stromal conditions, this adhesion phenotype was stable over multiple days, sorting cycles, and common across all epithelial tumor lines investigated. Weakly adherent cells displayed increased migration in both two-dimensional and three-dimensional migration assays; this was maintained for several days in culture...
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Journal: Cell Reports
Publication Identifier Type: DOI Publication Identifier: 10.1016/j.celrep.2021.108816
Volume: 34 Issue: 10 First Page #: 108816
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Publication Location:
Article Title: Adhesion strength and contractility enable metastatic cells to become adurotactic
Authors: Benjamin Yeoman, Gabriel Shatkin, Pranjali Beri, Afsheen Banisadr, Parag Katira, Adam J. Engler
Keywords: Cell Mechanics, Inter-cellular heterogeneity, cell migration, Cancer metastasis
Abstract: Significant changes in cell stiffness, contractility, and adhesion, i.e., mechanotype, are observed during a variety of biological processes. Whether cell mechanics merely change as a side effect of or driver for biological processes is still unclear. Here, we sort genotypically similar metastatic cancer cells into strongly adherent (SA) versus weakly adherent (WA) phenotypes to study how contractility and adhesion differences alter the ability of cells to sense and respond to gradients in material stiffness. We observe that SA cells migrate up a stiffness gradient, or durotax, while WA cells largely ignore the gradient, i.e., adurotax. Biophysical modeling and experimental validation suggest that differences in cell migration and durotaxis between weakly and strongly adherent cells are driven by differences in intra-cellular actomyosin activity. These results provide a direct relationship between cell phenotype and durotaxis.
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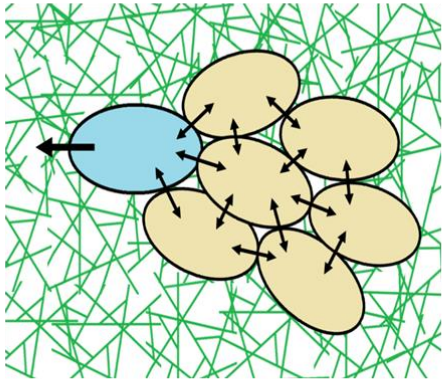
Journal: New Journal of Physics
Publication Identifier Type: DOI Publication Identifier: 10.1088/1367-2630/abf273
Volume: 23 Issue: 4 First Page #: 043034
Date Submitted: 4/26/21 12:00AM Date Published: 4/1/21 7:00AM
Publication Location:
Article Title: Anomalous cell sorting behavior in mixed monolayers discloses hidden system complexities
Authors: Paul Heine, Jürgen Lippoldt, Gudur Ashrith Reddy, Parag Katira, Josef A Käs
Keywords: Cell Mechanics, Self-Organization, Population Heterogeneity
Abstract: In tissue development, wound healing and aberrant cancer progression cell–cell interactions drive mixing and segregation of cellular composites. However, the exact nature of these interactions is unsettled. Here we study the dynamics of packed, heterogeneous cellular systems using wound closure experiments. In contrast to previous cell sorting experiments, we find non-universal sorting behavior. For example, monolayer tissue composites with two distinct cell types that show low and high neighbor exchange rates (i.e., MCF-10A & MDA-MB-231) produce segregated domains of each cell type, contrary to conventional expectation that the construct should stay jammed in its initial configuration. On the other hand, tissue compounds where both cell types exhibit high neighbor exchange rates (i.e., MDA-MB-231 & MDA-MB-436) produce highly mixed arrangements despite their differences in intercellular adhesion strength. The anomalies allude to a complex multi-parameter space underlying this sorting.
Distribution Statement: 2-Distribution Limited to U.S. Government agencies only; report contains proprietary info
Acknowledged Federal Support: **Y**

Partners

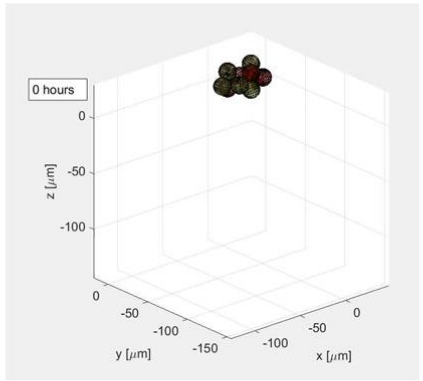
,

I certify that the information in the report is complete and accurate:
Signature: Parag Katira
Signature Date: 2/1/22 12:43AM

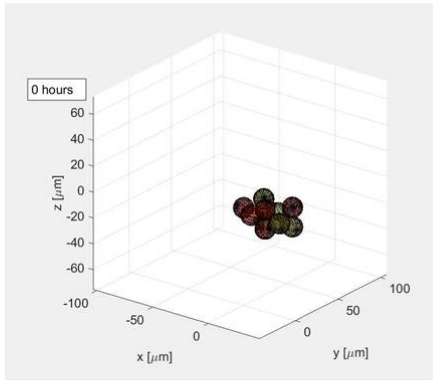
Collective Cell Migration in Heterogeneous 3D Fibrous Environments



Migrating clusters in a 3D matrix environment



A **single leader** drives the cluster onward



Switching between leaders **herds** the cluster

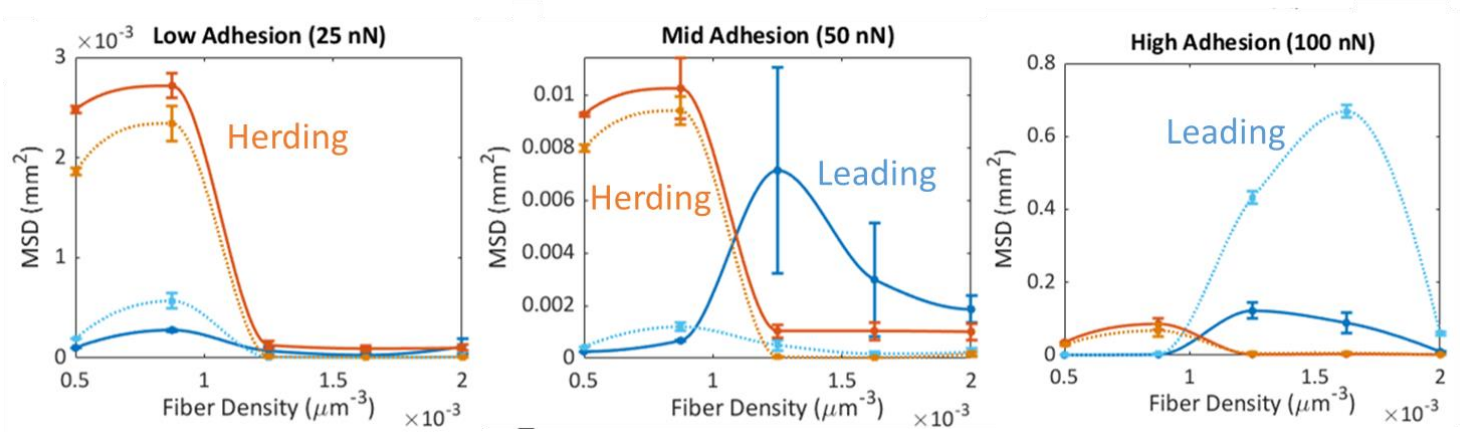


Figure 1: For cells with low-adhesion strength, herding promotes cluster lifetime and migration speed in low density environments. On the other hand, following a single leader promotes directed migration in high density fiber networks, but requires strong inter-cellular adhesion strength.

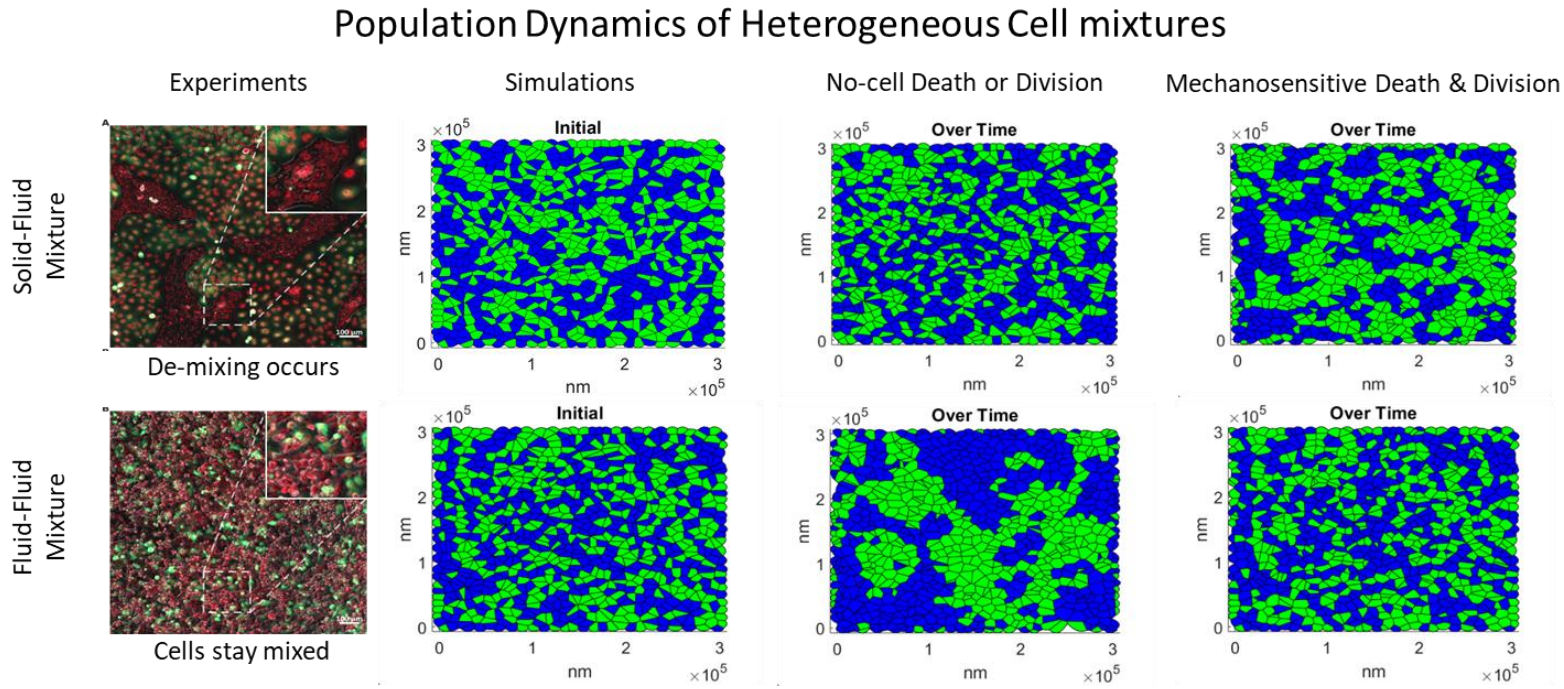


Figure 2. Soft cells form monolayers with fluid like properties. Stiff cells on the other hand form monolayers with solid like properties. However, mixtures of soft and stiff cells or soft and soft cells show unique and unexpected segregation and mixing behavior. Our computational models show that the unexpected dynamics can be explained by mechanosensitive cell death and division.

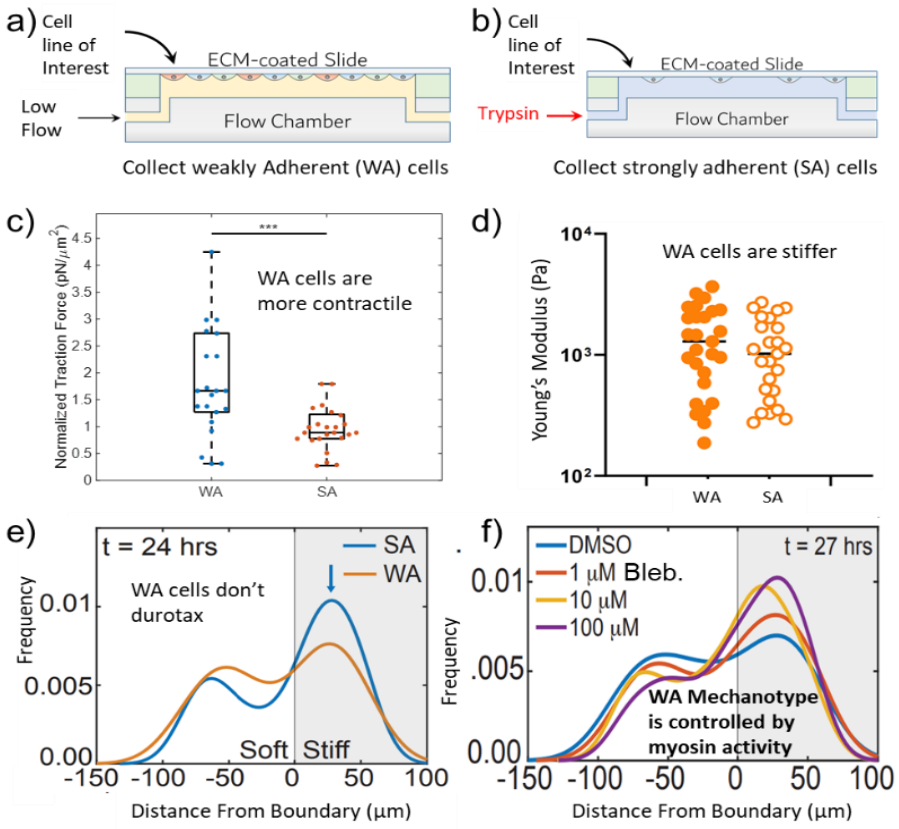
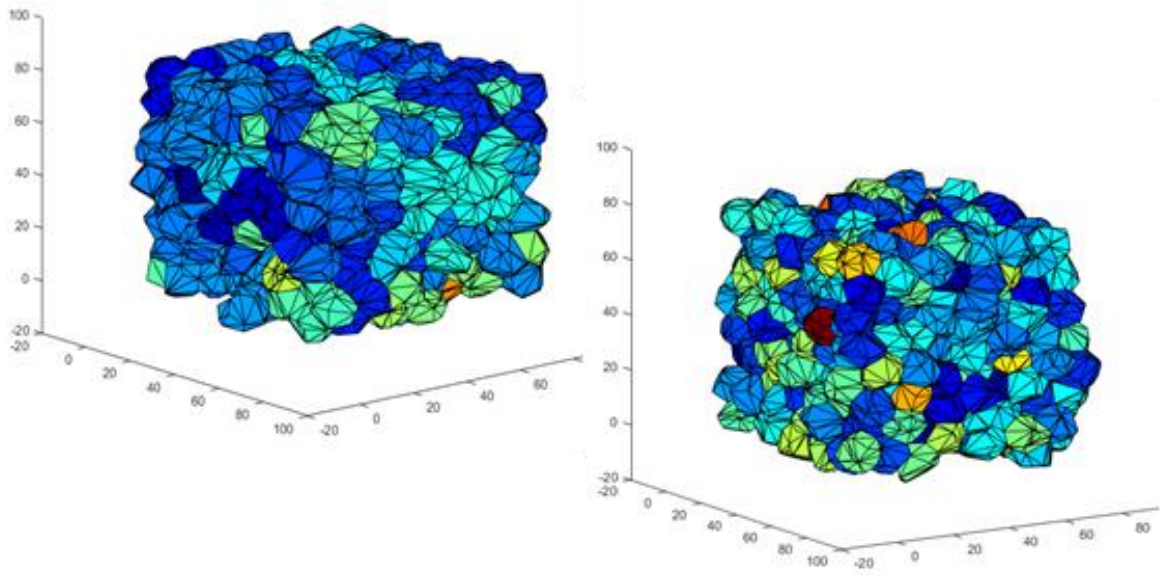


Figure 3. Weakly adherent cells (a) have increased contractility (c) and higher stiffness (d) compared to strongly adherent cells (b) as determined based on detachment under shear flow. The mechanotype controls migration and durotactic behavior (e) and is dependent on actin-myosin activity (f).



Tissue patchiness defined as ratio of local to global heterogeneity

$$c = \frac{-\sum P_i \ln(P_i) \Big/ \ln(N_{total})}{-\sum p_i \ln(p_i) \Big/ \ln(n_{cluster})}$$

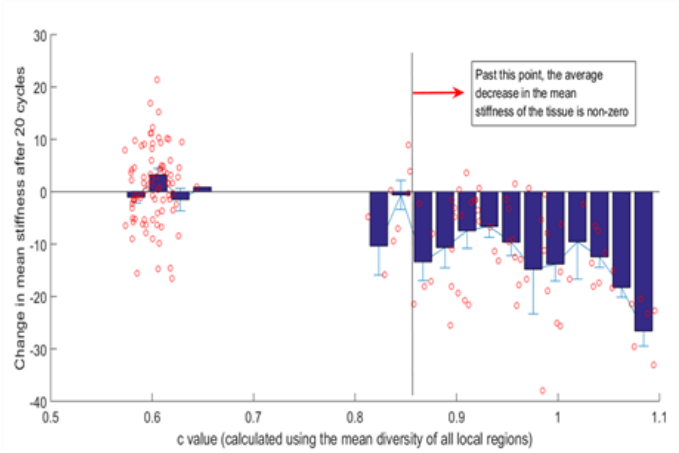


Figure 4. In heterogeneous 3D cell systems, the ratio of local to global heterogeneity can predict population stability. High ratio of local to global heterogeneity suggests a shift in population towards mechanically softer cells.