BIOGRAPHICAL SKETCH

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NAME: Hou, Chieh

eRA COMMONS USER NAME (credential, e.g., agency login): CHIEHHOU

POSITION TITLE: Research Scientist (PI)

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
National Taiwan University, Taipei, Taiwan	BS	06/2004	Physics
National Taiwan University, Taipei, Taiwan	MS	01/2007	Mechanical Eng.
Columbia University, New York, NY, USA	PHD	05/2018	Mechanical Eng.
University of Minnesota, Minneapolis, MN, USA	Postdoctoral Associate	08/2023	Biomedical Engineering

A. Personal Statement

Throughout my career and education, I have honed multiple computational and physical modeling skills, with a deep interest in understanding glioblastoma tumor progression. My aim is to establish myself as an expert in computational and physical modeling within experimental and clinical brain tumor research.

My interest in tissue and cell biomechanics began during my time at Robert Mauck's Laboratory at the University of Pennsylvania. Within a year, I developed a high-throughput mechanical device (Mohanraj et al. 2014) and investigated the stiffness and diffusivity of tissue constructs (Bian et al. 2013). Pursuing my passion for computational biomechanics, I joined Gerard Ateshian's lab at Columbia University as a Ph.D. student. During my Ph.D., we developed a novel multiphasic and multiscale cell-tissue model to study the mechanics, transport, and physiology of chondrocytes within cartilage (Hou et al. 2016; Hou et al. 2018). We implemented this model into the open-source finite element software, FEBio, using C++ programming.

To deepen my understanding of single-cell mechanics and physics, I joined David Odde's Laboratory at the University of Minnesota as a postdoc. During my postdoc, we developed the biophysical model Cell Migration Simulator (CMS), which was used to study cancer cell migration under various conditions: with different adhesion sizes (Hou et al. 2019), on viscoelastic substrates (Adebowale et al. 2021), on substrates with stiffness gradients (Isomursu et al. 2022), and within 1D channels (Lee et al. 2022). Recently, we applied the CMS to explore the physical and molecular mechanisms of heterogeneous cell migration in Mayo glioblastoma PDX cells, predicting their migration under drug treatments and correlating their RNAseq expressions to identify molecular biomarkers (Hou et al. 2024). We are currently studying the migration, pathology, and IHC staining of UMN glioblastoma patient-derived tumor cells using bioinformatics, regression methods, and machine learning algorithms (Hou et al. in preparation).

Now, as a junior faculty member in Neurosurgery at Brown University Health, my research goal is to establish computational and machine learning algorithms, along with experimental protocols, to study the tumor growth and diffusion in glioblastoma patients. My objective is to provide accurate, patient-specific estimates of tumor progression, aiding physicians and oncologists in optimizing treatment more effectively. This computational tool can be further developed to simulate tumor progression under various treatment modalities, offering a versatile platform that could inspire the development of novel treatment strategies for glioblastoma and other cancers.

1. Hou J, McMahon M, Sarkaria JN, et al (2024) Cell migration simulator-based biomarkers for glioblastoma. *Neuro-Oncology Advances* vdae184. https://doi.org/10.1093/noajnl/vdae184

2. Isomursu A, Park K-Y, Hou J, et al (2022) Directed cell migration towards softer environments. Nat Mater 21:1081–1090. https://doi.org/10.1038/s41563-022-01294-2. PMCID: PMC10712428

3. Hou JC, Shamsan GA, Anderson SM, et al (2019) Modeling distributed forces within cell adhesions of varying size on continuous substrates. Cytoskeleton (Hoboken) 76:571–585. https://doi.org/10.1002/cm.21561. PMID: 31512404

4. Lee SH, Hou JC, Hamidzadeh A, et al (2022) A molecular clock controls periodically driven cell migration in confined spaces. Cell Syst 13:514-529.e10. https://doi.org/10.1016/j.cels.2022.05.005. PMID: 35679858

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2023 - 2024	Researcher 5, University of Minnesota, Minneapolis, MN, USA, Biomedical Engineering
2018 - 2023	Postdoctoral Associate, University of Minnesota, Minneapolis, MN, USA, Biomedical Engineering
2012 - 2018	Research Assistance, Columbia University, New York, NY, USA, Mechanical Engineering
2011 - 2012	Research Engineer, University of Pennsylvania, Philadelphia, PA, USA, Orthopaedic Surgery
2010 - 2011	Teaching Assistant, National Taiwan University, Taipei, Taiwan, Mechanical Engineering
2007 - 2010	Associate Researcher, R&D Cencer, Sanyang Industry Co., Ltd, Hsinchu, Taiwan

Other Experience and Professional Memberships

2018 -	Member, Biomedical Engineering Society
2018 -	Member, American Society for Cell Biology

Honors

2023	Tenure Track Assistant Professor Offer, Utah State University Biological Engineering
2022	Impactful Research in UMN Postdoc Awards, UMN Postdoctoral Association
2021	UMN Brain Tumor Program Career Enhancement Awards, UMN Masonic Cancer Center, University of Minnesota
2018	PSOC Pilot Project Program Grant, UMN Physical Sciences in Oncology Center, University of Minnesota
2017	Image Based Biomedical Modeling (IBBM) Summer Course Fellowship, Scientific Computing and Imaging Institute, University of Utah
2015	Studying Abroad Scholarship, Ministry of Education, Taiwan
2015	Finalist in Student Paper Competition, C. Hou et al., Summer Biomechanics, Bioengineering and Biotransport Conference (SB3C 2015)
2014	Professional Development Scholarship, Engineering Graduate Student Council, Columbia University

C. Contribution to Science

a. Biophysics of glioblastoma cell migration

Glioblastoma is the most aggressive malignant brain tumor with poor survival due to its invasive nature driven by cell migration, with unclear linkage to transcriptomic information. We applied a physics-based motor-clutch model, a cell migration simulator (CMS), to parameterize the migration of glioblastoma cells and define physical biomarkers on a patient-by-patient basis. We reduced the 11-dimensional parameter space of the CMS into three principal physical parameters that govern cell migration: motor number –

describing myosin II activity, clutch number – describing adhesion level, and F-actin polymerization rate. Experimentally, we found that glioblastoma patient-derived (xenograft) (PD(X)) cell lines across mesenchymal (MES), proneural (PN), classical (CL) subtypes and two institutions (N=13 patients) had optimal motility and traction force on stiffnesses around 9.3kPa, with otherwise heterogeneous and uncorrelated motility, traction, and F-actin flow. By contrast, with the CMS parameterization, we found glioblastoma cells consistently had balanced motor/clutch ratios to enable effective migration, and that MES cells had higher actin polymerization rates resulting in higher motility. The CMS also predicted differential sensitivity to cytoskeletal drugs between patients. Finally, we identified 18 genes that correlated with the physical parameters, suggesting transcriptomic data alone could potentially predict the mechanics and speed of glioblastoma cell migration. We describe a general physics-based framework for parameterizing individual glioblastoma patients and connecting to clinical transcriptomic data, that can potentially be used to develop patient-specific anti-migratory therapeutic strategies.

a. Hou J, McMahon M, Sarkaria JN, et al (2024) Cell migration simulator-based biomarkers for glioblastoma. *Neuro-Oncology Advances* vdae184. https://doi.org/10.1093/noajnl/vdae184

2. Biophysics of cell migration

By the mid-2000s it was clear that a wide range of cell behaviors -including proliferation, apoptosis, migration, and differentiation- all depended strongly on the mechanical stiffness of the environment. However, we did not have a molecular-mechanical theory for how cells "know" how stiff their environment is. To address this issue, we developed a "motor-clutch" model, where myosin motors pull on F-actin that mechanically links to a compliant substrate through dynamic adhesion bonds. Using an integrated modeling-experimental approach, we found that the motor-clutch model successfully predicted a number of aspects of cell behavior as a function of mechanical stiffness. Of particular note, we found that the motor-clutch model naturally has an optimum, at which traction force is maximal, and that this optimum depends directly on the coordinate expression level of motors and adhesive clutches. Using this approach we discovered that cells can migrate toward softer environments, i.e. toward their optimum, which had not been reported previously.

a. Isomursu A, Park K-Y, Hou J, et al (2022) Directed cell migration towards softer environments. *Nat Mater* 21:1081–1090. https://doi.org/10.1038/s41563-022-01294-2. PMCID: PMC10712428

b. Lee SH, Hou JC, Hamidzadeh A, et al (2022) A molecular clock controls periodically driven cell migration in confined spaces. *Cell Syst* 13:514-529.e10. https://doi.org/10.1016/j.cels.2022.05.005. PMID: 35679858

c. Adebowale K, Gong Z, Hou JC, et al (2021) Enhanced substrate stress relaxation promotes filopodia-mediated cell migration. *Nat Mater* 20:1290–1299. https://doi.org/10.1038/s41563-021-00981-w. PMCID: PMC8390443

d. Hou JC, Shamsan GA, Anderson SM, et al (2019) Modeling distributed forces within cell adhesions of varying size on continuous substrates. *Cytoskeleton* (Hoboken) 76:571–585. https://doi.org/10.1002/cm.21561. PMID: 31512404

3. Multiphasic finite element modeling of cell and tissue

With the recent implementation of multiphasic materials in the open-source finite element (FE) software FEBio, three-dimensional (3D) models of cells embedded within the tissue may now be analyzed, accounting for porous solid matrix deformation, transport of interstitial fluid and solutes, membrane potential, and reactions. The cell membrane is a critical component in cell models, which selectively regulates the transport of fluid and solutes in the presence of large concentration and electric potential gradients, while also facilitating the transport of various proteins. The cell membrane is much thinner than the cell; therefore, in an FE environment, shell elements formulated as two-dimensional (2D) surfaces in

3D space would be preferred for modeling the cell membrane, for the convenience of mesh generation from image-based data, especially for convoluted membranes. However, multiphasic shell elements are yet to be developed in the FE literature and commercial FE software. We presented a novel formulation of multiphasic shell elements and its implementation in FEBio. The shell model includes front- and back-face nodal degrees-of-freedom for the solid displacement, effective fluid pressure and effective solute concentrations, and a linear interpolation of these variables across the shell thick- ness. This formulation was verified against classical models of cell physiology and vali- dated against reported experimental measurements in chondrocytes. This implementation of passive transport of fluid and solutes across multiphasic membranes makes it possible to model the biomechanics of isolated cells or cells embedded in their extracellular matrix (ECM), accounting for solvent and solute transport.

a. Hou JC, Maas SA, Weiss JA, Ateshian GA (2018) Finite Element Formulation of Multiphasic Shell Elements for Cell Mechanics Analyses in FEBio. *J Biomech Eng* 140:121009. https://doi.org/10.1115/1.4041043. PMCID: PMC10577663

b. Hou C, Ateshian GA (2016) A Gauss-Kronrod-Trapezoidal integration scheme for modeling biological tissues with continuous fiber distributions. *Comput Methods Biomech Biomed Engin* 19:883–893. https://doi.org/10.1080/10255842.2015.1075518. PMCID: PMC4807401

c. Mohanraj B, Hou C, Meloni GR, et al (2014) A high throughput mechanical screening device for cartilage tissue engineering. *J Biomech* 47:2130–2136. https://doi.org/10.1016/j.jbiomech.2013.10.043. PMCID: PMC4014530

d. Bian L, Hou C, Tous E, et al (2013) The influence of hyaluronic acid hydrogel crosslinking density and macromolecular diffusivity on human MSC chondrogenesis and hypertrophy. *Biomaterials* 34:413–421. https://doi.org/10.1016/j.biomaterials.2012.09.052. PMCID: PMC3578381