Indian Institute of Technology Delhi

DEPARTMENT OF BIOCHEMICAL ENGINEERING & BIOTECHNOLOGY

2017-18 Seminar Series

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Computational systems biology of cancer metastasis: can theory help understand cancer biology?

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Metastasis – the spread of cancer to distant organs through blood circulation – causes above 90% of all cancer-related deaths. To leave the home organ and enter the bloodstream, tumor cells lose epithelial traits such as cell-cell adhesion and gain the ability to migrate and invade – a process known as Epithelial-Mesenchymal Transition (EMT). Upon reaching distant organs, these cells stop migrating and regain cell-cell adhesion – a process called Mesenchymal-Epithelial Transition (MET). EMT and MET are largely considered as binary processes, and thus a hybrid epithelial/mesenchymal (E/M) phenotype has been tacitly assumed as transient.

Our integrated theoretical-experimental work suggests that a hybrid E/M phenotype can be stably maintained by cells, and can be more aggressive than purely epithelial or mesenchymal phenotype. I have developed novel mechanism-based mathematical models of regulatory networks underlying EMT or MET that predict that cells in a clonal population can attain different phenotypes – epithelial, mesenchymal and hybrid E/M – due to the systems-level emergent behavior of these networks. Moreover, these models predict that hybrid E/M cells are more likely to form metastases as compared to fully E or fully M ones, and have identified certain 'phenotypic stability factors' (PSFs) that can stabilize a hybrid E/M phenotype. These predictions have been validated experimentally in H1975 lung cancer cells that maintain a hybrid E/M phenotype stably and migrate collectively, a behavior that is impaired by knockdown of PSFs. Finally, higher levels of one or more PSFs associate with poor patient prognosis, thereby reinforcing that a hybrid E/M phenotype, but not necessarily a completely mesenchymal phenotype, may be considered as a hallmark of aggressiveness.

Collectively, my work highlights how an iterative crosstalk between theory and experiment can both generate novel insights into the dynamics of tumor progression and uncover previously unknown accelerators of metastasis.

All are welcome

Seminar will be held in DBEB SEMINAR ROOM at Block I, Room 232 at 4 PM
For additional information, contact Seminar coordinator D. Sundar at sundar@dbeb.iitd.ac.in

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RESEARCH AREAS

Computational Systems Biology, Mathematical Oncology, Quantitative modeling of biological networks, Physics of Cancer, Nonlinear Dynamics

EDUCATION

Rice University, Houston, TX, USA
Ph.D., Bioengineering — Aug 2012 – Sep 2016
Graduate Certificate in Teaching and Learning — Jan 2015 – May 2016

Indian Institute of Technology (IIT) Kanpur, Kanpur, India
M.Tech. (Master of Technology), Biological Sciences & Bioengineering (BSBE) — Aug 2010 – May 2012
B.Tech. (Bachelor of Technology), Biological Sciences & Bioengineering (BSBE) — Aug 2006 – May 2010

RESEARCH EXPERIENCE

Gulf Coast Consortia, Houston, TX
Postdoctoral Fellow, Computational Cancer Biology — Apr 2017 – present

Rice University, Houston, TX
Postdoctoral Fellow, Center for Theoretical Biological Physics — Oct 2016 – present
Graduate Student, Department of Bioengineering — Aug 2012 – Sep 2016

Genentech Inc., San Francisco, CA
Summer Intern — Jun 2016 – Aug 2016

IIT Kanpur, Kanpur, India
Masters' Student, Department of Biological Sciences & Bioengineering (BSBE) — Dec 2010 – Apr 2012

Johns Hopkins University, Baltimore, MD
Visiting Student, Department of Biomedical Engineering — May 2009 – Jul 2009

IIT Kanpur, Kanpur, India
Summer Undergraduate Research Grant for Excellence (SURGE) Fellow — May 2008 – Jul 2008

AWARDS AND HONORS

Winner, IBiology Young Scientist Series (YSS) — 2016
Overall 2nd place and People's Choice Award, SCREECH, Rice University — 2013
Summer Innovation Award, Biological Sciences & Bioengineering (BSBE), IIT Kanpur — 2009
SURGE (Summer Undergraduate Research Grant for Excellence) fellow, IIT Kanpur — 2008
2nd Best Poster Award, Gordon Research Conference on 'Physical Science of Cancer' — 2017
Landahl Travel Award, Society of Mathematical Biology Annual Meeting — 2017, 2015
IBB Travel Award, Institute of Biosciences and Bioengineering (IBB), Rice University — 2016, 2015
Travel Award, Rice University Graduate Student Association — 2015
Q-bio conference fellowship, Los Alamos National Laboratory — 2014
Best Poster Award, 10th Annual Computational and Theoretical Biology Symposium, Rice University — 2013

PEER-REVIEWED PUBLICATIONS (* denotes equal contribution, # denotes co-corresponding author)

(Google scholar metrics: Total citations – 709, h-index – 15, i10-index – 18)

Current postdoctoral work:

1. George JT*, **Jolly MK***, Xu S, Somarelli JA, Levine H (2017). Partial EMT based scoring metric for predicting cancer outcomes. **Cancer Research**, *in press*
2. **Jolly MK**[#], Boareto M, Debeb B, Aceto N, Farach-Carson MC, Woodward WA, Levine H[#] (2017). Inflammatory Breast Cancer: a model for investigating cluster-based dissemination. **NPJ Breast Cancer**, 3: 21
3. Kulkarni P, **Jolly MK**, Jia D, Mooney SM, Bhargava A, Kagohara LT, Chen Y, Hao P, He Y, Veltri RW, Grishaev A, Weninger K, Levine H, Orban J (2017). Phosphorylation-induced conformational dynamics in an intrinsically disordered protein and its potential role in phenotypic heterogeneity. **Proceedings of the National Academy of Sciences USA (PNAS)**, 114 (13): E2644-E2653
4. Jia D, **Jolly MK**, Harrison W, Boareto M, Ben-Jacob E, Levine H (2017). Operating principles of tristable circuits regulating cellular differentiation. **Physical Biology**, 14: 035007
5. Jia D, **Jolly MK**, Tripathi SC, Hollander DP, Huang B, Lu M, Celiktas M, Ramirez-Pena E, Ben-Jacob E, Onuchic JN, Hanash SM, Mani SA, Levine H (2017). Distinguishing mechanisms underlying EMT Tristability. **Cancer Convergence**, *in press*
6. **Jolly MK**, Tripathi SC, Somarelli JA, Hanash SM, Levine H (2017). Epithelial-mesenchymal plasticity: how have quantitative mathematical models helped improve our understanding? **Molecular Oncology**, 11 (7): 739-754
7. **Jolly MK**, Ware K, Gilja S, Somarelli JA, Levine H (2017). EMT and MET: necessary or permissive for metastasis? **Molecular Oncology**, 11 (7): 755-769
8. **Jolly MK**, Ward C, Eapen MS, Myers S, Hallgren O, Levine H, Sohal S (2017). Epithelial mesenchymal transition (EMT), a spectrum of states: role in both lung development and disease. **Developmental Dynamics** (PubMed ID: 28646553)
9. **Jolly MK**, Levine H. Computational systems biology of epithelial-hybrid-mesenchymal transitions (2017). **Current Opinion in Systems Biology**, 3: 1-6
10. Jia D, **Jolly MK**, Kulkarni P, Levine H. Phenotypic plasticity and cell-fate decisions in cancer: insights from dynamical systems theory. **Cancers**, 9 (7): 70
11. Mooney SM*, Talebian V*, **Jolly MK***, Jia D*, Gromala M, Levine H, McConkey BJ (2017). GRHL2/ZEB feedback loop – a key axis in the regulation of EMT in breast cancer. **Journal of Cellular Biochemistry**, 118 (9): 2559-2570
12. Tripathi SC, Fahrmann JF, Celiktas M, Aguilar M, Marini KM, **Jolly MK**, Katayama H, Wang H, Murage EN, Dennison JB, Watkins N, Levine H, Ostrin EJ, Taguchi A, Hanash SM. MCAM mediates chemoresistance in small cell lung cancer via PI3K/AKT/SOX2 Signaling Pathway. **Cancer Research**, 77 (16): 4414-4425
13. Evans MK, Brown M, Geradts J, Robinson TJ, **Jolly MK**, Vermeulen PB, Palmer G, Gromeier M, Levine H, Morse MA, van Laere SJ, Devi GR. Crosstalk between MNK and XIAP mediates NFkB activity to promote a hyperproliferative breast cancer phenotype (under revision in **Cancer Research**)
14. Kulkarni A, Jolly MK, Sengupta K. Twist1 overexpression induces genome instability in colorectal cancer cells. (under revision in **Oncotarget**)

15. Bocci F*, **Jolly MK***, Tripathi SC*, Aguilar M, Hanash SM, Levine H, Onuchic JN. Numb inhibits a complete EMT by modulating Notch signaling. (under review in **Journal of the Royal Society Interface**)

16. **Jolly MK**, Weninger K, Levine H, Orban J, Kulkarni P. Phenotypic plasticity, bet-hedging, and androgen independence in prostate cancer: role of non-genetic heterogeneity. (under review in **Nature Reviews Urology**)

Graduate research (Ph.D.) work:

17. Ware KE, Gilja S, Xu S, Shetler S, **Jolly MK**, Wang X, Bartholf-Dewitt S, Hish AJ, Jordan S, Eward W, Levine H, Armstrong AJ, Somarelli JA (2017). Induction of mesenchymal-epithelial transitions in sarcoma cells. **Journal of Visualized Experiments** (PMID: 28448023)

18. Somarelli JA, Shelter S, **Jolly MK**, Wang S, Bartholf-Dewitt S, Hish A, Gilja S, Eward W, Ware K, Levine H, Armstrong AJ, Garcia-Blanco MA (2016). Mesenchymal-epithelial transition in sarcomas is controlled by the combinatorial expression of GRHL2 and miR-200s. **Molecular and Cellular Biology**, 36 (19): 2503-13 **(Cover article)**

19. Boareto M, **Jolly MK**, Goldman A, Pietila M, Mani SA, Sengupta S, Ben-Jacob E, Levine H, Onuchic JN (2016). Notch -Jagged signaling can give rise to clusters of cells exhibiting a hybrid epithelial/mesenchymal phenotype. **Journal of the Royal Society Interface**, 13 (118): 20151106

20. **Jolly MK,** Tripathi SC, Jia D, Mooney SM, Celiktas M, Mani SA, Hanash S, Pienta KJ, Ben-Jacob E, Levine H (2016). Stability of the hybrid epithelial /mesenchymal phenotype. **Oncotarget**, 7 (19): 27067-27084

21. Tripathi SC, Peters HL, Taguchi A, Katayama H, Wang H, Momin A, **Jolly MK**, Celiktas M, Rodriguez-Canales J, Liu H, Behrens C, Wistuba II, Ben-Jacob E, Levine H, Molldrem JJ, Hanash SM, Ostrin EJ (2016). Immuno-proteasome deficiency is a feature of non-small cell lung cancer with a mesenchymal phenotype and is associated with a poor outcome. **Proceedings of the National Academy of Sciences USA (PNAS)**, 113 (11): E1555-1564

22. Mooney SM, **Jolly MK**, Levine H, Kulkarni P (2016). Phenotypic plasticity in prostate cancer: the role of intrinsically disordered proteins. **Asian Journal of Andrology**, 18 (5): 704-10

23. Grigore AD*, **Jolly MK***, Jia D, Farach-Carson MC, Levine H (2016). Tumor budding: the name is EMT. Partial EMT. **Journal of Clinical Medicine**, 5(5): E51

24. Huang B, **Jolly MK**, Lu M, Tsarfaty I, Ben-Jacob E, Onuchic JN (2015). Modeling the transitions between collective and solitary migration phenotypes in cancer metastasis. **Scientific Reports**, 5: 17379 *(Recommended by F1000 faculty)*

25. Boareto M, **Jolly MK**, Ben-Jacob E, Onuchic JN (2015). Jagged mediates differences in normal and tumor angio-genesis by affecting tip-stalk fate decision. **Proceedings of the National Academy of Sciences USA (PNAS),** 112 (29): E3836-E3844

26. **Jolly MK***, Jia D*, Boareto M, Mani SA, Pienta KJ, Ben-Jacob E, Levine H (2015). Coupling the modules of EMT and stemness: A tunable 'stemness window' model. **Oncotarget,** 6(28): 25161-25174

27. **Jolly MK***, Boareto M*, Lu M, Clementi C, Onuchic JN, Ben-Jacob E (2015). Operating principles of Notch-Delta-Jagged module of cell-cell communication. **New Journal of Physics***,* 17: 055021

28. Jia D*, **Jolly MK***, Boareto M, Parsana P, Mooney SM, Pienta KJ, Levine H, Ben-Jacob E (2015). OVOL guides the epithelial-hybrid-mesenchymal transition. **Oncotarget***,* 6 (17): 15436-15448

29. **Jolly MK**, Boareto M, Huang B, Jia D, Lu M, Onuchic JN, Ben-Jacob E, Levine H (2015). Implications of the hybrid epithelial/mesenchymal phenotype in metastasis. **Frontiers in Oncology**,5: 155

30. Boareto M, **Jolly MK**, Lu M, Onuchic JN, Clementi C, Ben-Jacob E (2015). Jagged-Delta Asymmetry in Notch Signaling can give rise to a Sender/Receiver hybrid phenotype, **Proceedings of the National Academy of Sciences USA (PNAS)**, 112 (5): E402-E409
31. **Jolly MK**, Huang B, Lu M, Mani SA, Levine H, Ben-Jacob E (2014). Towards elucidating the connection between epithelial-mesenchymal transitions and stemness, **Journal of the Royal Society Interface**, 11 (101): 20140962 *(Highlighted in National Science Foundation (NSF) News)*
32. Huang B, Lu M, **Jolly MK**, Tsarfaty I, Onuchic JN, Ben-Jacob E (2014). The three-way switch operation of Rac1/ RhoA GTPase-based circuit controlling amoeboid-hybrid-mesenchymal transition, **Scientific Reports** 4: 6449
33. Lu M*****, **Jolly MK***, Onuchic JN, Ben-Jacob E (2014). Toward Decoding the Principles of Cancer Metastasis Circuits. **Cancer Research,** 74 (17): 4574-4587
34. Lu M*****, **Jolly MK***, Levine H, Onuchic JN, Ben-Jacob E (2013). MicroRNA-based regulation of epithelial-hybrid-mesenchymal cell fate determination. **Proceedings of the National Academy of Sciences USA (PNAS),** 110 (45): 18144-18149
35. Lu M, **Jolly MK**, Gomoto R, Huang B, Onuchic JN, Ben-Jacob E (2013). Tristability in Cancer Associated miRNA-TF Chimera Toggle Switch. **Journal of Physical Chemistry B,** 117 (42): 13164-13174

M. Tech. work:

36. **Jolly MK*,#**, Rizvi MS*, Kumar A, Sinha P# (2014). Mathematical modeling of sub-cellular asymmetry of Fat-Dachsous Heterodimer for generation of Planar Cell Polarity, **PLoS ONE** 9(5): e97641

Book chapters:

1. **Jolly MK**, Li X, Levine H. Collective effects in cancer progression. MIT press, *in press*
2. **Jolly MK**, Jia D, Levine H. Modeling cell-fate decisions in biological systems: bacteriophages, hematopoietic stem cells, epithelial-to-mesenchymal transition, and beyond. **Quantitative Biology: Theory, Computational Models and examples of models.** MIT press, *in press*
3. Jia D, Jolly MK, Levine H. Uses of bifurcation analysis in understanding cellular decision-making. **Quantitative Biology: Theory, Computational Models and examples of models.** MIT press, *in press*

CONFERENCES, SEMINARS, WORKSHOPS

Talks:

1. Hybrid epithelial/mesenchymal phenotype – the 'metastatic sweet spot'. *8th Annual Physics of Cancer Symposium*, Leipzig, Germany, October 2017 (scheduled)
2. Quantifying epithelial-mesenchymal plasticity in cancer and its association with poor survival. *18th International Conference on Systems Biology*, Blacksburg, August 2017
3. Quantifying epithelial-mesenchymal plasticity during cancer progression. *Annual Meeting of Society of Mathematical Biology,* Salt Lake City, July 2017
4. Mathematical modeling in cancer biology: can theory help understand cancer? *Hematology/Oncology Grand Rounds, Duke University*, Durham, April 2017
5. Stability and stemness of a hybrid epithelial/mesenchymal phenotype. *American Association for Cancer Research (AACR) Annual Meeting*, April 2017
6. Inflammatory Breast Cancer: a model for investigating cluster-based dissemination. *10th Annual Morgan Welch Inflammatory Breast Cancer Meeting, UT MD Anderson Cancer Center*, February 2017
7. Implications of hybrid epithelial/mesenchymal phenotype in metastasis: how can theory help understand cancer biology better. *Philippines Genome Center (Webinar),* June 2016

8. Network motifs that stabilize the hybrid epithelial/mesenchymal phenotype. *American Physical Society (APS) March Meeting*, Baltimore, March 2016
9. Clusters of circulating tumor cells: primary 'bad agents' of metastasis. *9th Annual q-bio Summer School*, Fort Collins, July 2015
10. Modeling the phenotypic plasticity of metastatic cancer stem cells. *Annual Meeting of Society of Mathematical Biology,* Atlanta, July 2015
11. Looking at epithelial plasticity from a physicist's perspective. *University of Texas Health Science Center*, Houston, October 2014
12. United we stand, divided we fall: Advantages of collective cell migration to cancer. *8th Annual q-bio Meeting*, Santa Fe, August 2014

Workshops/Summer Schools Attended:

1. 8th Annual q-bio Summer School (Theme: Stochastic Gene Regulation), Albuquerque, July 2014
2. SERC School on Introduction to Systems and Synthetic Biology, IIT Bombay, April-May 2012

Poster Presentations:

1. Quantifying epithelial-mesenchymal plasticity and its association with patient survival. *11th Annual q-bio Meeting*, Rutgers University, July 2017
2. Implications of stable hybrid epithelial/mesenchymal phenotype in cancer metastasis. *Keystone Meeting on Cell Plasticity within the Tumor Microenvironment*, Big Sky, January 2017
3. Coupling the Decision-making of EMT and Stemness: A Flexible 'Stemness Window' Model. *CPRIT Conference on Innovations in Cancer Prevention and Research*, Austin, November 2015
4. Stemness and stability in the hybrid epithelial/mesenchymal phenotype*. 2nd Annual Hallmarks of Cancer Symposium*, Rice University, Houston, October 2015
5. Stemness in the hybrid epithelial/mesenchymal phenotype. *Gordon Research Conference (GRC) on Stem Cells and Cancer,* Ventura, February 2015
6. Coupled decision-making of EMT and stemness: a bottom-up regulatory model. *American Association for Cancer Research (AACR) meeting on Computational & Systems Biology*, San Francisco, February 2015
7. Stemness in epithelial, hybrid epithelial/mesenchymal and mesenchymal phenotypes. *11th Annual Computational and Theoretical Biology Symposium*, Rice University, December 2014
8. Modeling the association between epithelial-mesenchymal transition (EMT) and stemness. *8th Annual q-bio Meeting*, Santa Fe, August 2014
9. Characterizing the hybrid epithelial/mesenchymal phenotype: collective migration of carcinoma cells. *1st Annual Bioengineering Graduate Student Symposium*, Rice University, May 2014
10. Hybrid Epithelial/Mesenchymal Phenotype and Epithelial Plasticity: Role of (miR-200/ZEB). *105th Annual Meeting of American Association for Cancer Research (AACR)*, San Diego, April 2014
11. Tristable 'three-way' miR-TF toggle switch: The hybrid epithelial/mesenchymal phenotype. Meeting on *Translating Cancer Data and Models to Clinical Practice*, Institute for Pure & Applied Mathematics, UCLA, Los Angeles, February 2014
12. Tristability in miR-TF toggle switch: The hybrid epithelial/mesenchymal phenotype. 10th *Annual Computational and Theoretical Biology Symposium (CTBS)*, Rice University, Houston, December 2013
13. Mathematical modeling of global regulation of PCP in Drosophila. *International Conference on Mathematical and Theoretical Biology*, Pune, January 2012
14. Modeling the global regulation of Planar Cell Polarity in wing epithelium. *12th International Conference on Systems Biology (ICSB)*, Heidelberg/Mannheim, August 2011
15. Keeping the hair aligned: Mathematical modeling of global module of Planar Cell Polarity. *International Conference on Mathematical Biology*, Indian Institute of Science, Bangalore, July 2011

TEACHING AND ADVISING EXPERIENCE

Guest Lecturer, BIOE/C 4/560 (Cancer Biology), Rice University 2017, 2016
- Delivered an invited lecture to students introducing them to mathematical modeling approaches relevant to cancer

Fellowship Coach, Office of Graduate and Postdoctoral Studies (GPS), Rice University 2015 – 2016
- Mentored graduate students for fellowships such as NSF Graduate Research Fellowship Programme (GRFP)

Mentor, Frontiers in Science (FIS) - Summer Undergraduate Research Program 2015
- Guided the research project for an undergraduate student from the University of Houston

Peer Consultant, Center for Written, Oral and Visual Communication (CWOVC), Rice University 2014 – 2016
- Mentored more than 100 students across disciplines in effective academic communication (abstracts, manuscripts, seminars, essays, personal statements, dissertation chapters) via one-to-one consultation sessions
- Designed and conducted a four-week workshop on 'Communicating Science to non-experts' for graduate students and postdoctoral fellows across different disciplines

Teaching Assistant, BIOE 372 (Biomechanics), Rice University 2014
- Conducted guest lectures, designed and taught recitation sections, held office hours, managed 3 UG graders

Teaching Assistant, BIOE 322 (Fundamentals of Systems Physiology), Rice University 2013
- Designed and taught recitation sessions, held office hours

Teaching Assistant, BIOE 444 (Mechanical Lab Testing Module), Rice University 2013
- Oversaw 10 UG students run mechanical testing experiments, held office hours, graded lab reports and final project

PROFESSIONAL MEMBERSHIP AND SERVICE

Associate Member, American Association for Cancer Research (AACR) May 2013-present
Student Member, Society for Mathematical Biology (SMB) March 2015-present
Student Member, American Physical Society August 2015-present

Reviewed manuscripts for Bioinformatics, Scientific Reports, Journal of Laboratory Automation, Tumor Biology, Oncotarget, Journal of Cancer
Organizer, mini-symposium on 'Quantifying phenotypic plasticity in cancer cells' at the Annual Meeting of Society of Mathematical Biology, Salt Lake City July 2017

LEADERSHIP EXPERIENCE

Founder Co-Chair, ComSciCon Houston 2017 2016 – 2017
- Conceptualized the inaugural science communication conference (ComSciCon) in the state of Texas
- Led a team of 20 PhD students and postdocs across Houston in planning and execution of the conference

Graduate Student Association (GSA) Representative, Indian Students at Rice, Rice University 2013 – 2014
- Secured funding over $2000 for 5 cultural events; co-organized the key cultural event attended by over 200 people

President, Student's Gymkhana, IIT Kanpur 2009 – 2010
- Initiated 'President Hour' for information dissemination among the student community and getting their feedback
- Conducted and chaired 'Open House' sessions for involving students in institutional decision-making processes

Co-founder and Editor-in-Chief, NERD (quarterly campus science magazine at IIT Kanpur) 2008 – 2010
- Led a team of students in fruitful science journalism, and managed the content, design and layout of 8 issues

- Interviewed eminent scientists such as Dr. Martin Chalfie (Nobel Laureate, 2008, Chemistry) and Dr. R Chidambaram (Principal Scientific Advisor, Government of India); interviews were published in NERD
- Secured funding from Dean, R&D over INR 4,00,000 as a student project for printing 8 issues over 2 years

REFERENCES

Herbert Levine
Hasselmann Professor of Bioengineering; Co-Director, Center for Theoretical Biological Physics (CTBP)
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