

Conference Program Book

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<http://easychair.org-smart-program/ICSB2017/index.html>)

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and

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Department of Computer Science,
Department of Biological Sciences,
Departments of Biological Systems Engineering, Mathematics, and Physics
Academy of Integrated Science (AIS),
BioComplexity Institute (BI),
Fralin Institute (FI),
Virginia Tech Carilion Research Institute (VTCRI),
Institute for Critical Technology and Applied Science (ICTAS)



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Co-chair: Xueyang Feng (BioEngineering department, Virginia Tech)
Co-chair: John J Tyson (Biological Sciences department, Virginia Tech)

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Chair: Tyson, John VT

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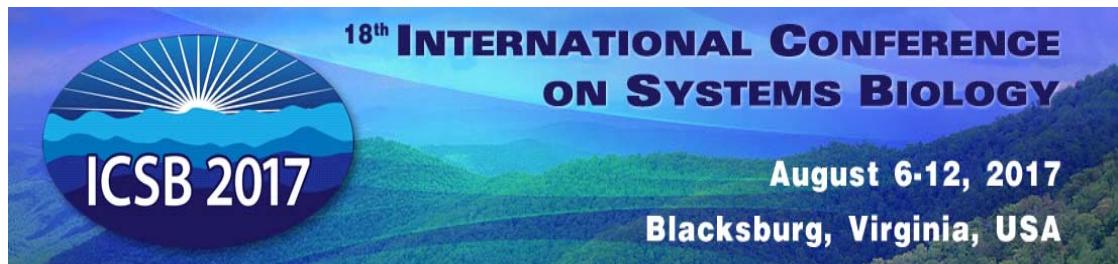


Keynote Speakers:

Naama Barkai Weizmann Institute of Science, Israel https://barkai-serv.weizmann.ac.il	Bela Novak Oxford University, UK https://www.bioch.ox.ac.uk/aspsite/index.asp?pageid=593	Xiaoliang Sunney Xie Harvard University, USA & Peking University, China https://bernstein.harvard.edu/pages/AboutProfXie.html

Plenary Speakers:

Frank Doyle Harvard University http://doyle.seas.harvard.edu	Tim Elston UNC-Chapel Hill http://www.med.unc.edu/pharm/elstonlab	Lingchong You Duke Univ https://bme.duke.edu/faculty/lingchong-you
Thomas Hoefer DKFZ Heidelberg http://www.dkfz.de/en/modellierung-biologischer-systeme/	Edda Klipp Humboldt Univ, Berlin https://www2.hu-berlin.de/biologie/theorybp/	Ursula Kummer Univ Heidelberg http://www.cos.uni-heidelberg.de/index.php/u.kummer?l=de
Sylvia Plevritis Stanford http://med.stanford.edu/plevritis.htm	Uwe Sauer ETH Zuerich http://www.imsb.ethz.ch/research/sauer.html	Hiroki Ueda RIKEN, Japan http://www.cdb.riken.jp/lsb/index.html
1		



Jianhua Xing Univ Pittsburgh https://www.csb.pitt.edu/jianhua-xing/	Yvonne Chen UCLA http://yvchen.bol.ucla.edu	Kevin Janes Univ Virginia http://bme.virginia.edu/janes/
Julio Saez-Rodriguez (RWTH Aachen) http://www.combine.rwth-aachen.de/index.php/people-detail/julio-saez-rodriguez.html	Nick Buchler Duke http://buchler.phy.duke.edu	Chris Barrett Virginia Tech https://www.bi.vt.edu/faculty/Christopher-Barrett
Carla Finkielstein Virginia Tech http://www.biol.vt.edu/faculty/finkielstein/	Keren Lasker Stanford University https://profiles.stanford.edu/keren-lasker	Anre Levchenko Yale Univ http://levchenkolab.yale.edu

Leslie M. Loew UConn Health http://facultydirectory.uhc.edu/profile?profileId=Loew-Leslie		Jae Kyoung Kim KAIST, Korea http://mathsci.kaist.ac.kr/~jaekkim/



Sunday, August 6		
Time	Event	Location
08:00 - 17:00	Registration	Squires - Williamsburg Room
09:00 - 18:00	Session 1A: Combined Tutorial - Modeling and Simulation Tools in Systems Biology	Squires - Brush Mountain A & B
09:00 - 18:00	Session 1B: Tutorial - Metabolic flux modeling and computer aided strain design with cobrapy, cameo, and DDDeCaF	Squires - Colonial
09:00 - 18:00	Session 1C: Workshop: The PATRIC bioinformatics resource center for omic data analysis	Squires - Old Dominion Ballroom
09:00 - 18:00	Session 1D: Workshop: Multi-scale metabolic modeling and engineering	Goodwin Hall, Room 190
12:30 - 18:30	Session 2: Tutorial: 4th International Hands-on Tutorial on Logical Modeling	Torgersen Hall - Room 1010
13:00 - 18:00	Session 3: Tutorial: Network Dynamics and Cell Physiology (first session)	Torgersen Hall - Room 3100

Monday, August 7		
Time	Event	Location
08:00 - 17:00	Registration	Squires - Williamsburg Room
08:30 - 12:00	Session 4A: Workshop: Quantitative Systems Pharmacology	Squires - Colonial
08:30 - 12:00	Session 4B: Tutorial: Network Dynamics and Cell Physiology (continued)	Squires - Brush Mountain A & B
08:30 - 12:00	Session 4C: Tutorial: GraphSpace: Interdisciplinary Collaborations in Network Biology	Torgersen Hall - Room 1010
08:30 - 12:00	Session 4D: COPASI Tutorial	BioComplexity Institute Room 118
08:30 - 12:00	Session 4E: Tutorial: Mathematical and computational foundations of infectious disease epidemiology	BioComplexity Institute
08:30 - 12:00	Session 4F: Workshop: Developing Tutorials For Research Tools And Methods	Torgersen Hall - Room 3100
08:30 - 12:00	Session 4G: Workshop on Drug Response Measurement and Analysis	Torgersen Hall - Room 1060
09:00 - 12:00	Session 5: StochSS: An Integrated Development Environment for Simulation and Analysis of Discrete Stochastic Biochemical Models	Torgersen Hall - Room 1020
12:00 - 13:30	Lunch	Squires - Commonwealth Ballroom
13:30 - 16:30	Session 6: Monday Afternoon	Squires - Colonial
16:30 - 18:30	Session 7A: Parallel Session I a: Synthetic Biology	Squires - Brush Mountain A & B
16:30 - 18:30	Session 7B: Parallel Session I b: Cellular Signaling Networks I	Squires - Room 342



16:30 - 18:30	Session 7C: Parallel Session I c: Omics Technol & Application	Squires - Colonial
18:30 - 20:30	Session 8: Welcome Reception and a Keynote Speech	Squires - Old Dominion Ballroom

Tuesday, August 8		
Time	Event	Location
08:00 - 17:00	Registration	Squires - Williamsburg Room
08:30 - 10:30	Session 9: Tuesday Morning	Squires - Colonial
10:30 - 12:30	Session 10A: Parallel Session II a: Multicellular Systems Biology	Squires - Brush Mountain A & B
10:30 - 12:30	Session 10B: Parallel Session II b: Cancer Systems Biology I	Squires - Room 342
10:30 - 12:30	Session 10C: Parallel Session II c: Cellular Signaling Networks II	Squires - Old Dominion Ballroom
12:30 - 14:00	Lunch	Squires - Commonwealth Ballroom
14:00 - 16:30	Session 11: Tuesday Afternoon	Squires - Colonial
16:30 - 18:30	Session 12A: Parallel Session III a: Cellular Signaling Networks III	Squires - Brush Mountain A & B
16:30 - 18:30	Session 12B: Parallel Session III b: Cancer Systems Biology II	Squires - Room 342
16:30 - 18:30	Session 12C: Parallel Session III c: Special Session Due to Schedule Limitation	Squires - Old Dominion Ballroom
18:30 - 20:30	Session 13: Poster Session I & Reception	Squires - Commonwealth Ballroom

Wednesday, August 9		
Time	Event	Location
08:00 - 17:00	Registration	Squires - Williamsburg Room
08:30 - 10:30	Session 14: Wednesday Moring	Squires - Colonial
10:30 - 12:30	Session 15A: Parallel Session IV a: Developmental Dynamics and Control	Squires - Brush Mountain A & B
10:30 - 12:30	Session 15B: Parallel Session IV b: Cell Decision Making I	Squires - Room 342
10:30 - 12:30	Session 15C: Parallel Session IV c: NeuroScience	Squires - Old Dominion Ballroom
12:30 - 14:00	Lunch	Squires - Commonwealth Ballroom
14:00 - 19:00	Session : Free Time and Excursions	Squires - Alumni Mall Entrance
19:00 - 21:00	Session : Conference Dinner	The Inn at Virginia Tech - Latham Ballroom



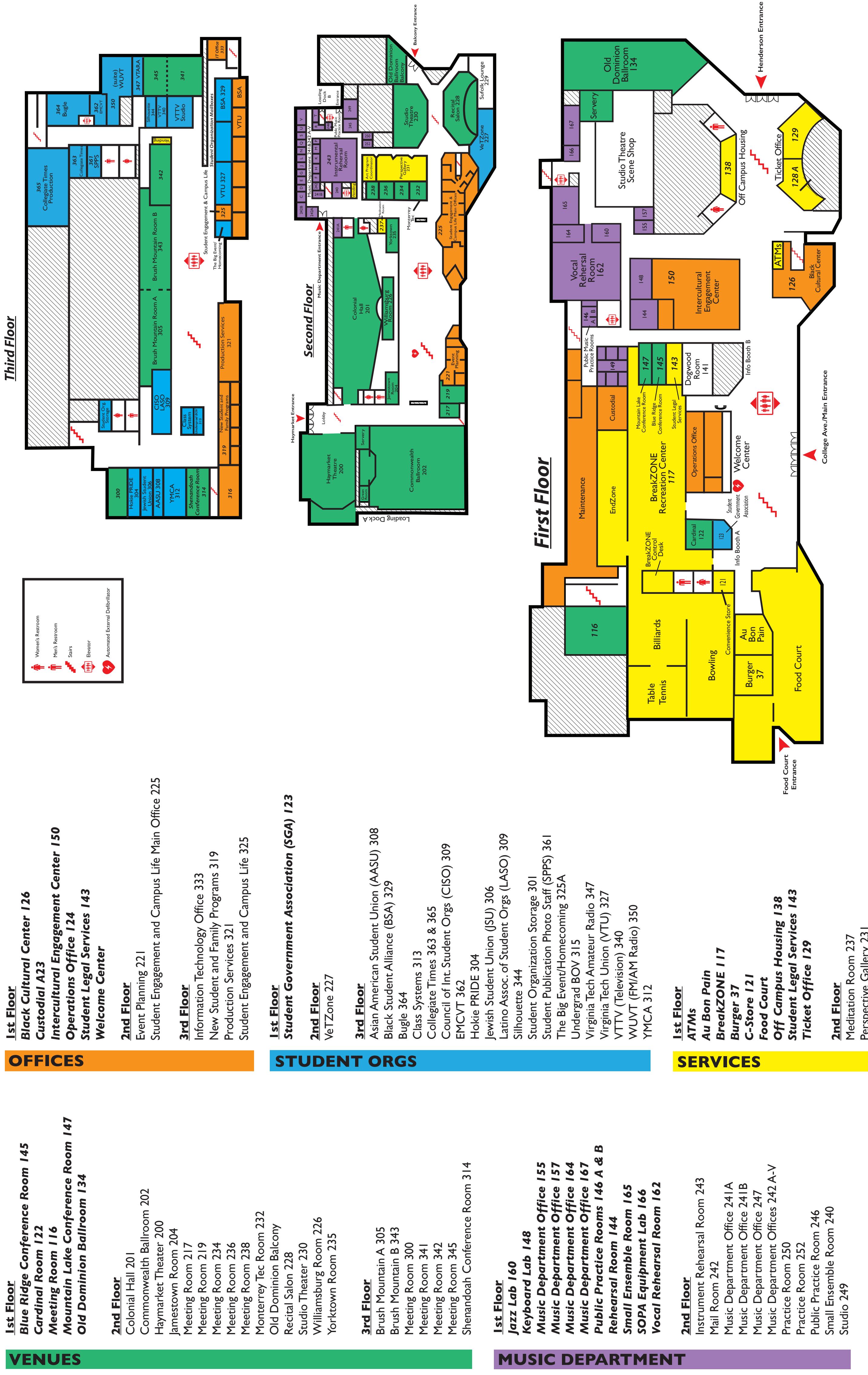
Thursday, August 10

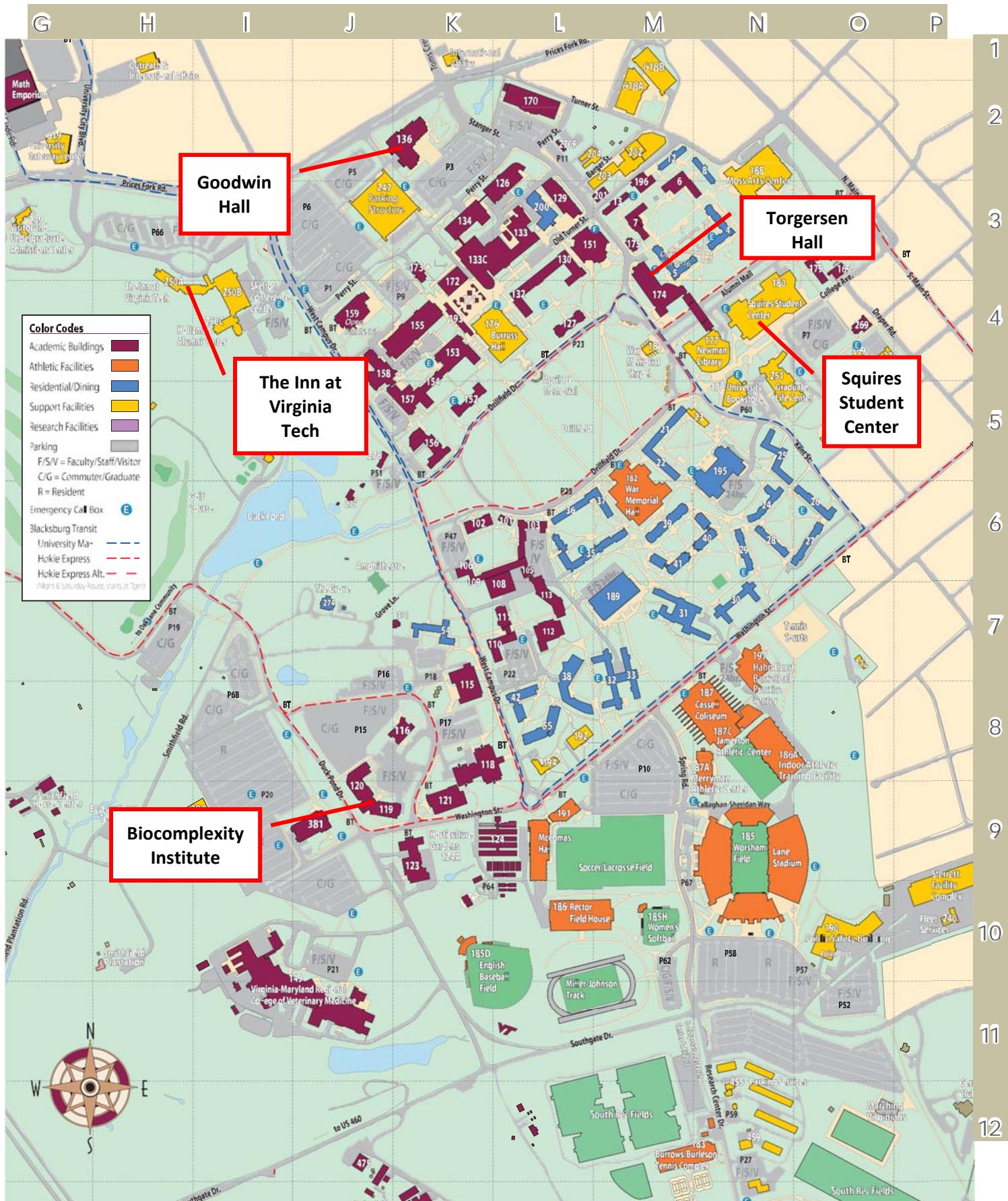
Time	Event	Location
08:00 - 10:00	Registration	Squires - Williamsburg Room
08:30 - 10:30	Session 16: Thursday Morning	Squires - Colonial
10:30 - 12:30	Session 17A: Parallel Session V a: Emerging Technologies	Squires - Brush Mountain A & B
10:30 - 12:30	Session 17B: Parallel Session V b: Computational Methodology I	Squires - Room 342
10:30 - 12:30	Session 17C: Parallel Session V c: Cell Decision Making II	Squires - Old Dominion Ballroom
12:30 - 14:00	Lunch	Squires - Commonwealth Ballroom
14:00 - 16:30	Session 18: Thursday Afternoon	Squires - Colonial
16:30 - 18:30	Session 19A: Parallel Session VI a: Regulatory Network I	Squires - Brush Mountain A & B
16:30 - 18:30	Session 19B: Parallel Session VI b: Computational Methodology II	Squires - Room 342
16:30 - 18:30	Session 19C: Parallel Session VI c: Cellular Variability	Squires - Old Dominion Ballroom
18:30 - 20:30	Session : Poster Session II & Reception	Squires - Commonwealth Ballroom

Friday, August 11

Time	Event	Location
08:30 - 10:30	Session 20: Friday Morning	Squires - Colonial
10:30 - 12:30	Session 21A: Parallel Session VII a: Systems Biology Education	Squires - Colonial
10:30 - 12:30	Session 21B: Parallel Session VII b: Regulatory Network II	Squires - Room 342
10:30 - 12:30	Session 21C: Parallel Session VII c: Computational Methodology III	Squires – Old Dominion Ballroom
12:30 - 14:00	Lunch	Squires - Commonwealth Ballroom
14:00 - 15:00	Session : Special Session: Career Development in Systems Biology	Squires - Colonial
15:00 - 16:00	Session : Closing Remarks & Coffee Break	Squires - Colonial

SQURIES STUDENT CENTER





Alphabetical Key

K-7.....109.....Agnew Hall
 M-2.....204.....Air Conditioning Plant
 M-8.....33.....Ambler Johnston Hall - East Wing
 M-8.....32.....Ambler Johnston Hall - West Wing
 O-4.....368.....Architecture Annex
 O-4.....269.....Armory
 M-2.....196.....Art and Design Learning Center
 O-6.....26.....Barringer Hall
 J-9.....119.....Bioinformatics Facility Phase 1
 J-9.....120.....Bioinformatics Facility Phase 2
 K-3.....173.....Bishop-Favro Hall
 M-3.....5.....Brodie Hall
 L-2.....270F.....Building 270F [VPAS-IT]
 M-3.....270G.....College of Science
 Administration Building
 K-4.....171.....Burchard Hall
 L-4.....176.....Burress Hall
 L-6.....37.....Campbell Hall - East Wing
 L-6.....36.....Campbell Hall - Main Wing
 N-8.....187.....Cassell Coliseum
 L-7.....112.....Cheatham Hall
 L-8.....38.....Cochrane Hall
 K-3.....172.....Cowgill Hall
 K-5.....156.....Davidson Hall
 K-4.....155.....Derring Hall
 M-7.....189.....Dietrick Hall
 L-2.....126.....Durham Hall
 M-5.....23.....Eggleston Hall - East Wing
 M-5.....21.....Eggleston Hall - Main Wing
 M-5.....22.....Eggleston Hall - West Wing
 L-7.....110.....Engel Hall
 K-10.....185D.....English Baseball Field
 J-12.....475.....Etgen Dairy Pavilion
 M-3.....13.....Femoyer Hall
 P-10.....240.....Fleet Services
 J-9.....123.....Food Science and Technology
 L-7.....111.....Fralin Biotechnology Center
 K-4.....193.....G. Burke Johnston Student Center
 I-5.....295.....Golf Course Club House
 O-5.....251.....Graduate Life Center at Donaldson Brown
 L-9.....124.....Greenhouse
 Q-10.....241.....Grounds Building (Central Stores)
 K-2.....136.....Goodwin Hall
 J-4.....158.....Hahn Hall - North Wing
 K-5.....157.....Hahn Hall - South Wing
 N-7.....197.....Hahn Hurst Basketball Practice
 Facility
 K-3.....133C.....Hancock Hall
 L-8.....42.....Harper Hall
 I-10.....149C.....Harry T. Peters Animal Clinic
 N-12.....459.....Health & Safety Building
 O-3.....179.....Henderson Hall
 K-7.....54.....Hillcrest Hall
 L-3.....130.....Holden Hall
 H-4.....250A.....Holtzman Alumni Center
 J-9.....381.....Human and Agricultural
 Biosciences Building I
 L-6.....103.....Hutcheson Hall
 K-8.....116.....Institute for Critical Technology
 and Applied Science II (ICTAS II)
 N-12.....183.....Indoor Tennis Courts
 N-8.....187C.....Jamerson Athletic Center
 N-6.....28.....Johnson Hall
 L-3.....129.....Kelly Hall
 M-3.....1.....Lane Hall
 N-9.....185.....Lane Stadium
 L-7.....113.....Latham Hall
 L-3.....200.....Lavery Hall
 N-7.....30.....Lee Hall
 M-3.....175.....Liberal Arts Building
 K-9.....121.....Life Sciences I Facility

K-8.....118.....Litton-Reaves Hall
 M-3.....7.....Major Williams Hall
 M-3.....151.....McBryde Hall
 L-9.....191.....McComas Hall
 O-4.....369.....Media Annex
 P-4.....370.....Media Building
 N-8.....187A.....Merryman Athletic Facility
 O-6.....27.....Miles Hall
 M-2.....203.....Military Building/Laundry
 N-2.....8.....Monteith Hall
 N-2.....188.....Moss Arts Center
 L-8.....55.....New Hall West
 N-6.....40.....New Residence Hall East
 N-6.....24.....Newman Hall
 N-4.....177.....Newman Library
 L-4.....132.....Norris Hall
 M-2.....618A.....North End Center
 M-1.....618B.....North End Center Garage
 N-6.....29.....O'Shaughnessy Hall
 M-3.....201.....Old Security Building
 N-5.....195.....Owens Hall
 K-4.....153.....Pamplin Hall
 N-12.....455.....Parking Services
 L-4.....127.....Patton Hall
 M-6.....39.....Payne Hall
 N-3.....4.....Pearson Hall
 M-6.....41.....Peddrew-Yates Residence Hall
 M-2.....202.....Power House
 K-6.....102.....Price Hall
 M-7.....31.....Pritchard Hall
 O-10.....190.....Public Safety Building
 L-3.....133.....Randolph Hall
 L-10.....186.....Rector Field House
 I-11.....149B.....Richard B. Talbot Educational
 Resources Center
 K-5.....154.....Robeson Hall
 L-6.....101.....Sandy Hall
 K-6.....106.....Saunders Hall
 L-7.....108.....Seitz Hall
 N-2.....6.....Shanks Hall
 I-9.....380.....Southwest Chiller Plant
 M-6.....35.....Slusher Hall
 L-8.....194.....Smith Career Center
 L-6.....105.....Smyth Hall
 J-6.....275.....Solitude
 N-4.....180.....Squires Student Center
 P-10.....242.....Sterrett Facility Complex
 L-8.....192.....Student Services Building
 L-2.....170.....Surge Space Building
 J-7.....274.....The Grove [President's House]
 O-3.....169.....Theater 101
 M-2.....12.....Thomas Hall
 M-4.....174.....Torgerson Hall
 N-5.....178.....University Bookstore
 O-5.....252.....University Club
 N-5.....25.....Vawter Hall
 J-11.....149.....Virginia-Maryland Regional
 College of Veterinary Medicine
 G-3.....249.....Visitors & Undergraduate
 Admissions Center
 K-7.....301.....Wallace Annex
 K-8.....115.....Wallace Hall
 M-4.....181.....War Memorial Chapel
 M-6.....182.....War Memorial Gymnasium
 K-3.....134.....Whittemore Hall
 J-11.....149A.....William E. Lavery Health
 Research Center
 K-5.....152.....Williams Hall
 M-10.....185H.....Women's Softball Field
 J-5.....276.....Wright House
 O-7.....272.....417 Clay Street

Numerical Key

M-3.....1.....Lane Hall
 N-3.....4.....Pearson Hall
 M-3.....5.....Brodie Hall
 N-2.....6.....Shanks Hall
 M-3.....7.....Major Williams Hall
 N-2.....8.....Monteith Hall
 M-2.....12.....Thomas Hall
 M-3.....13.....Femoyer Hall
 M-5.....22.....Eggleston Hall
 N-6.....24.....Newman Hall
 N-5.....25.....Vawter Hall
 O-6.....26.....Barringer Hall
 O-6.....27.....Miles Hall
 N-6.....28.....Johnson Hall
 N-6.....29.....O'Shaughnessy Hall
 N-7.....30.....Lee Hall
 M-7.....31.....Pritchard Hall
 M-8.....32.....Ambler Johnston Hall
 M-6.....35.....Slusher Hall
 L-6.....36.....Campbell Hall
 L-8.....38.....Cochrane Hall
 M-6.....39.....Payne Hall
 N-6.....40.....New Residence Hall East
 M-6.....41.....Peddrew-Yates Res. Hall
 L-8.....42.....Harper Hall
 K-7.....54.....Hillcrest Hall
 L-8.....55.....New Hall West
 L-6.....101.....Sandy Hall
 K-6.....102.....Price Hall
 L-6.....103.....Hutcheson Hall
 L-6.....105.....Smyth Hall
 K-6.....106.....Saunders Hall
 L-7.....108.....Seitz Hall
 K-7.....109.....Agnew Hall
 L-7.....110.....Engel Hall
 L-7.....111.....Fralin Life Science Institute
 L-7.....112.....Cheatham Hall
 L-7.....113.....Latham Hall
 K-8.....115.....Wallace Hall
 K-8.....116.....Institute for Critical Technology
 and Applied Science II (ICTAS II)
 K-8.....118.....Litton-Reaves Hall
 J-9.....119.....Bioinformatics Phase I
 J-9.....120.....Bioinformatics Phase II
 K-9.....121.....Life Sciences I
 J-9.....123.....Food Science and Technology
 L-9.....124.....Greenhouses
 K-9.....124A.....Hahn Horticulture Gardens
 L-2.....126.....Durham Hall
 L-4.....127.....Patton Hall
 L-3.....129.....Kelly Hall
 L-3.....130.....Holden Hall
 L-4.....132.....Norris Hall
 L-3.....133.....Randolph Hall
 K-3.....133C.....Hancock Hall
 K-3.....134.....Whittemore Hall
 K-2.....136.....Goodwin Hall
 J-11.....149.....Virginia-Maryland Regional
 College of Veterinary Medicine
 J-11.....149A.....William E. Lavery Health
 Research Center
 I-11.....149B.....Richard B. Talbot Educational
 Resources Center
 I-10.....149C.....Harry T. Peters Animal Clinic
 M-3.....151.....McBryde Hall
 K-5.....152.....Williams Hall
 K-4.....153.....Pamplin Hall
 K-5.....154.....Robeson Hall
 K-4.....155.....Derring Hall
 K-5.....156.....Davidson Hall
 K-5.....157.....Hahn Hall - South Wing
 J-4.....158.....Hahn Hall - North Wing

UNIVERSITY NUMBERS AND ADDRESSES

All area codes 540

General Switchboard231-6000

Admissions

Undergraduate 925 Prices Fork Road231-6267
Graduate Graduate Life Center at Donaldson Brown231-6691
 www.grads.vt.edu

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Cooperative Extension 101 Hutcheson Hall231-5299
Human Resources Northend Center231-9331
Inn at Virginia Tech231-8000
International Students Harper Hall231-6527
Outreach and International Affairs University Gateway Center231-3205

Parking Services 455 Tech Center Dr.231-3200
 Research 301 Burruss Hall231-6077

Skelton Conference Center231-8000

Student Affairs 112 Burruss Hall231-6272

University Relations 314 Burruss Hall231-5396

Visitor Information Center231-3548

Academic Colleges

Agriculture and Life Sciences 1060 Litton-Reaves Hall231-6503
Architecture and Urban Studies 202 Cowgill Hall231-6416
Engineering 3046 Torgerson Hall231-6641
Liberal Arts and Human Sciences 260 Wallace Hall231-6779
Natural Resources and Environment 138 Cheatham Hall231-5482
Pamplin Business 1046 Pamplin Hall231-6602
Science North End Center231-5422
Veterinary Medicine Phase II Bldg.231-4699

ICSB 2017: INTERNATIONAL CONFERENCE ON SYSTEMS BIOLOGY 2017

PROGRAM INDEXES

PROGRAM FOR SUNDAY, AUGUST 6TH

Days: next day all days

View: [session overview](#) [talk overview](#)

08:00-17:00 Session : Registration

LOCATION: Williamsburg Room

09:00-18:00 Session 1A: Tutorial: COMBINE Tutorial -
Modelling and Simulation Tools in Systems Biology

For more details, please see

<http://co.mbine.org/events/tutorial2017>

CHAIR: [Martin Golebiewski](#)

LOCATION: Brush Mountain A & B

09:00 [Martin Golebiewski](#), [Frank Bergmann](#), [Akira Funahashi](#),
[Ron Henkel](#), [Noriko Hiroi](#), [Stefan Hoops](#), [Ursula Kummer](#), [Leslie Loew](#), [Pedro Mendes](#), [Jürgen Pahle](#), [Sven Sahle](#) and [Andreas Weidemann](#)

COMBINE Tutorial - Modelling and Simulation Tools in Systems Biology

SPEAKER: [Martin Golebiewski](#)

ABSTRACT. Participants will learn how to set up computer models of biological systems (e.g. metabolic or signalling networks) using experimental kinetic data and how to simulate them in different systems biology platforms. Hands-on sessions, lectures and software demonstrations will be included, providing attendees with the necessary skills to access experimental kinetics data from available resources, to assemble computer models with these data, and finally to simulate the generated models using simulation tools. Also handling and exchange of biological models based on existing community standards will be demonstrated along with the basic principles of the underlying standard formats.

Topics:

- Model setup using different software tools and systems biology platforms
- Using experimental data for setting up quantitative models
- Parameter estimation, optimization and model fitting
- Simulation, analysis and visualization of biochemical models
- Database supported modelling: integrated data

- management and model databases
- Community standards and formats for systems biology models

Target audience:

Experimentalists and modellers with some very basic experience in modelling and simulation of biological networks and everybody who would like to learn more about the tools and standards. Attendees are expected to bring their own computer for hands-on training.

Covered tools, platforms and databases:

- CellDesigner: <http://www.celldesigner.org/>
- COPASI: <http://www.copasi.org>
- JWS Online: <http://jiji.biochem.sun.ac.za/>
- SABIO-RK: <http://sabio.h-its.org/>
- SEEK: <http://fair-dom.org/platform/seek/>
- Virtual Cell (VCell): <http://vcell.org>

Introduced standard formats:

Some commonly used community standards for model and modelling data exchange, as well as for model visualization will be introduced (SBGN, SBML and SED-ML) in practical examples using the covered tools. More information about the standards can be found on the **COMBINE (Computational Modeling in Biology Network)** website: <http://co.mbine.org>

Tutors:

- Akira Funahashi and Noriko Hiroi:** [Keio University](#) (Yokohama, Japan)
- Martin Golebiewski, Ron Henkel and Andreas Weidemann:** [HITS, Heidelberg](#) (Germany)
- Stefan Hoops:** [Biocomplexity Institute of Virginia Tech](#) (Blacksburg, Virginia, USA)
- Ursula Kummer, Frank Bergmann, Jürgen Pahle and Sven Sahle:** [University of Heidelberg](#) (Germany)
- Leslie M. Loew:** [UConn Health - Richard D. Berlin Center for Cell Analysis and Modeling](#) (Farmington, CT, USA)
- Pedro Mendes:** [UConn Health - Center for Quantitative Medicine](#) (Farmington, CT, USA)

09:00-18:00 Session 1B: Tutorial: Metabolic flux modeling and computer aided strain design with cobrapy, cameo and DD-DeCaF

CHAIR: [Henning Redestig](#)

LOCATION: Colonial Hall

09:00 [Henning Redestig, Nikolaus Sonnenschein, Zachary King, Moritz Beber](#) and [Danny Dannaher](#)

Tutorial: Metabolic flux modeling and computer

aided strain design with cobrapy, cameo and DD-DeCaF
SPEAKER: [Henning Redestig](#)

ABSTRACT. Good software is essential for most modern systems biology applications. Part of the growing cobrapy community, the freely available Python packages cobrapy, cameo and escher together implement numerous popular visualization, analysis and simulation methods for metabolic flux models, as well as search and optimization algorithms for designing novel pathways.

The cobrapy software collection lays a stable foundation for constraints-based modeling and strain design using a popular language that additionally boasts a wide array of packages for data handling, visualization and application development. In this full-day tutorial, we first give an introduction to the web-based graphical interface that is based on these packages, the data-driven design of cell factories and communities platform (DD-DeCaF), and then proceed to provide programming examples using the Jupyter notebook. Participants of all backgrounds are welcome, prior programming experience is not required.

09:00-18:00 Session 1C: Workshop: The PATRIC bioinformatics resource center for omic data analysis

CHAIR: [Rebecca Wattam](#)

LOCATION: Old Dominion Ballroom

09:00 [Rebecca Wattam](#)

The PATRIC bioinformatics resource center for omic data analysis

SPEAKER: [Rebecca Wattam](#)

ABSTRACT. Resource Center (BRC) (<https://www.patricbrc.org>). PATRIC provides a necessary “first-step” for any Systems Biology or Omics data exploration. Established by the National Institute of Allergy and Infectious Diseases (NIAID) in 2004, PATRIC provides researchers with an online resource that stores and integrates a variety of data types—e.g. genomics, transcriptomics, protein–protein interactions, 3D protein structures and sequence typing data, and associated metadata. Currently, PATRIC has more than 93,000 bacterial genomes, more than 1000 archaeal genomes, and genomic data for 10 eukaryotic organisms that include humans, mice and rats. PATRIC has expanded and improved its research capabilities for users by building and incorporating a set of services that are designed to streamline and simplify common bioinformatic workflows. These services include genome assembly, genome annotation, RNA-Seq analysis, expression import, proteome comparison, metabolic model reconstruction and variation analysis. All of these services are available through a private workspace that allows users to compare their private

data to any of the public data in the PATRIC database. Researchers can upload their data files (e.g. sequence reads, assembled genomes, transcriptomic data), run the desired analysis services, integrate their private data with the data in PATRIC for comparative analysis, store the resulting output files and download the results.

09:00-18:00 Session 1D: Workshop: Multi-scale metabolic modeling and engineering

For details, please see the link:

<https://register.cpe.vt.edu/search/publicCourseSearchDetails.do?method=load&courseld=520618>

CHAIR: [Justin Barone](#)

LOCATION: Goodwin Hall, Room 190

09:00 [Justin Barone](#)

Workshop: Multi-scale metabolic modeling and engineering

SPEAKER: [Justin Barone](#)

ABSTRACT. A need for the ability to apply fundamental mathematical models to current industrial fermentation processes was identified. These models would not be empirical and would help industrial researchers increase processing efficiencies. Since the models would be fundamental, they would better connect the molecular to the macroscopic scales, which is currently lacking in the industry. In other words, it is anticipated that the workshop will be the first meeting of academic and industrial researchers on this advanced metabolic engineering topic and that eventually, metabolic models applied to industrial fermentation processes will connect molecules to titer to increase efficiency. Industrial researchers are really good at empirical models derived from experiments. However, what does not exist in the bioprocessing industry is the use of fundamental models where metabolic processes are described from the ground up using the latest technology in metabolic engineering. These techniques are only now being taught at universities at the advanced undergraduate and graduate levels so most current industrial researchers have not been exposed to these metabolic engineering techniques. Metabolic modeling techniques could help the pharmaceutical, chemical, and fuel industries.

12:30-18:30 Session 2: Tutorial: 4th International Hands-on Tutorial on Logical Modeling

CHAIR: [Tomas Helikar](#)

LOCATION: Torgersen Hall - Room 1010

12:30 [Tomas Helikar](#) and [Julio Saez-Rodriguez](#)

Workshop: 4th International Hands-on Tutorial on Logical Modeling

SPEAKER: [Tomas Helikar](#)

ABSTRACT. The motivation of this tutorial is to provide hands-on experience with several logical modeling software tools. This tutorial will be made accessible to participants with no modeling experience as well as to those who are seasoned modelers.

Logical modeling provides a computational approach to the visualization and analysis of the dynamics of biochemical and biological systems complementary to others such as reaction-based or rule-based modeling. One of the main advantages of logical models is their scalability and the relatively easy method of construction. In part due to these attributes, logical models have become increasingly more popular among the computational biology community. This has, in turn, led to the development of different techniques and software tools that enable the construction, simulation, and analysis of logical models and their variants (Boolean, multilevel, deterministic, stochastic, etc.) to address various biological questions.

This workshop aims at extending the outreach of the logical modeling community (namely, the Consortium for Logical Modelling and Tools, CoLoMoTo, colomoto.org), and providing an overview of recent achievements in tool development that render possible the modeling and the analysis of large cellular networks, covering intricate signaling pathways, sophisticated transcriptional networks, as well as novel regulatory mechanisms.

Specifically, two hands-on tutorials will cover the Cell Collective (www.cellcollective.org) and CellNOpt (www.cellnopt.org) software tools.

13:00-18:00 Session 3: Tutorial: Network Dynamics and Cell Physiology (first session)

CHAIRS: [Bela Novak](#) and [John Tyson](#)

LOCATION: Torgersen Hall - Room 3100

13:00 [John Tyson](#) and [Bela Novak](#)

Network Dynamics and Cell Physiology

SPEAKER: [John Tyson](#)

ABSTRACT. A major theme of the International Conference on Systems Biology will be mathematical models of the molecular regulatory networks that underlie cell signaling, cell differentiation, cell growth and division, cell stress responses, cancer cell development, and other aspects of cell physiology. Because we expect many ‘newcomers’ to be attending the conference, it seems appropriate to hold an introductory tutorial on mathematical modeling on Sunday afternoon and Monday morning before the conference begins. The tutorial will be taught by two pioneers of the field, Professors John Tyson and Bela Novak, who have worked together for 25 years on mathematical models of cell growth and division, who have published some of the foundational papers in the

field, and who have written several highly cited tutorial papers on “network dynamics and cell physiology”. The tutorial will combine lecture-style instruction with hands-on problem solving and computer exercises.

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ICSB 2017: INTERNATIONAL CONFERENCE ON SYSTEMS BIOLOGY 2017

PROGRAM INDEXES

PROGRAM FOR MONDAY, AUGUST 7TH

Days: [◀ previous day](#) [next day ▶](#) [all days ↻](#)

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08:00-17:00 Session : Registration

LOCATION: Williamsburg Room

08:30-12:00 Session 4A: Workshop: Quantitative Systems Pharmacology

CHAIR: [Valeriu Damian](#)

LOCATION: Colonial Hall

08:30 [Valeriu Damian](#), [Eric Sobie](#), [Loveleena Bansal](#),
[Jonathan Wagg](#), [Kapil Gadkar](#) and [Saroja Ramanujan](#)

Quantitative Systems Pharmacology

SPEAKER: [Valeriu Damian](#)

ABSTRACT. Quantitative Systems Pharmacology (QSP) has been described as “the quantitative analysis of the dynamic interactions between drug(s) and a biological system to understand the behaviour of the system as a whole, as opposed to the behaviour of its individual constituents,” (van der Graaf and Benson, Pharm Res, 2011). In 2011, an NIH working group on QSP issued a white paper espousing the idea that improving the success of pharmaceutical research and development can in part be accomplished by reinvigorating the field of pharmacology “by introducing concepts, methods and investigators from computational biology, systems biology and biological engineering, thereby allowing modern pharmacologists to apply systems-level ideas to practical problems in drug development. QSP has deep roots in classical pharmacology and physiology but adds a molecule and systems-level approach that allows drug responses to be studied in the context of increasing knowledge of the complex and subtle interconnectedness of signaling, transcriptional and metabolic networks, as well as the variation in individual patients arising from differences in genetics and environment.” QSP has been gaining traction in the biopharmaceutical industry, in academic departments and professional organizations in pharmaceutical sciences, and recently, with regulatory agencies as well (Peterson and Riggs, CPT-PSP 2015). However, further advancing this field requires continued close interaction of the QSP community with the systems biology and biological engineering communities. As such, we propose that a workshop on QSP at ICSB, highlighting how systems

biology approaches can be leveraged in the context of systems pharmacology, can enrich both fields and further collaborative work in this area that is proving increasingly valuable in pharmaceutical research and development.

**Schedule: Quantitative Systems Pharmacology -
Mon Aug 7, 8:30am-noon**

8:30 Opening remarks by Valeriu Damian
(GlaxoSmithKline)

8:45 Quantitative Systems Pharmacology and Toxicology - QSP & QST : An overview by Valeriu Damian (GlaxoSmithKline)

9:15 Bridging the gap between Systems Biology and QSP: Application on modeling the Complement pathway and evaluating treatments for autoimmune diseases by Loveleena Bansal (GlaxoSmithKline)

9:45 Break

10:00 Complementary Systems Pharmacology approaches to dissecting PI3K-inhibitor dependent GI toxicity (part 1) by Jonathan Wagg (Roche)

10:30 Complementary Systems Pharmacology approaches to dissecting PI3K-inhibitor dependent GI toxicity (part 2) by Kapil Gadkar(Genentech)

11:00 Integrated transcriptomics and mathematical modeling analysis for quantitative predictions of drug-induced toxicity. by Eric Sobie (Mount Sinai School of Medicine)

11:30 Panel Discussion: Challenges in bridging Systems Biology with Quantitative Systems Pharmacology and Toxicology by All speakers

12:00 Session ends

Participants List:

Chair Valeriu
Damian, GlaxoSmithKline damiav01@gsk.com

Co-Chair Eric Sobie, Mount Sinai School of Medicine, eric.sobie@mssm.edu

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Cell Physiology (continued)

CHAIRS: [Bela Novak](#) and [John Tyson](#)

LOCATION: Brush Mountain A & B

08:30-12:00 Session 4C: Tutorial: GraphSpace:
Interdisciplinary Collaborations in Network Biology

CHAIR: [Tm Murali](#)

LOCATION: Old Dominion Ballroom

08:30 [T. M. Murali](#) and [Aditya Bharadwaj](#)

Tutorial: GraphSpace: Interdisciplinary Collaborations in Network Biology

SPEAKER: [T. M. Murali](#)

ABSTRACT. Computational analysis of molecular interaction networks has become pervasive in systems biology. Nearly every publication that uses network analysis includes a visualization of a graph in which the nodes and edges are laid out in two dimensions. Several systems implement methods for creating such layouts. Despite these advances, interdisciplinary research teams in network biology face several challenges in sharing, exploring, and interpreting computed networks in their collaborations.

GraphSpace is a web-based system that provides a rich set of user-friendly features designed to enhance network-based collaboration:

- Users can upload richly-annotated networks, irrespective of the algorithms or software used to generate them.
- Users can create private groups, invite other users to join groups, and share networks with group members.
- A user may search for networks that contain a specific node or edge, or a collection of nodes and edges.
- A powerful layout editor allows users to efficiently modify node positions, edit node and edge styles, save new layouts, and share them with other users.
- Researchers may make networks public and provide a persistent URL in a publication, enabling other researchers to explore these networks.

This tutorial will provide an in-depth introduction to GraphSpace. Attendees will receive hands-on training on the GraphSpace web interface and how to incorporate programmatic interaction with GraphSpace into their network analysis projects.

08:30-12:00 Session 4D: COPASI Tutorial

CHAIR: [Stefan Hoops](#)

LOCATION: BioComplexity Institute Room 118

08:30 [Stefan Hoops](#), [Ursula Kummer](#), [Pedro Mendes](#), [Sven Sahle](#), [Jürgen Pahle](#), [Brian Klahn](#) and [Frank Bergman](#)

COPASI Tutorial

SPEAKER: [Stefan Hoops](#)

ABSTRACT. COPASI is a software application for simulation and analysis of biochemical networks. It is developed jointly by the groups of Pedro Mendes, Ursula Kummer, Sven Sahle, and Stefan Hoops and is freely available for academic and commercial use.

COPASI's current features include stochastic and deterministic time course simulation, steady-state analysis (including stability), metabolic control analysis, elementary mode analysis, mass conservation analysis, import and export of SBML level 1 - 3, optimization, parameter scanning and parameter fitting. It runs on MS Windows, Linux, and Mac OS X

We will use COPASI to explain how the modelling, simulation and computational analysis of biochemical systems works. We will also critically evaluate the limitations of different simulation methods.

08:30-12:00 Session 4E: Tutorial: Mathematical and computational foundations of infectious disease epidemiology

CHAIR: [Bryan Lewis](#)

LOCATION: Torgersen Hall - Room 1010

08:30 [Bryan Lewis](#), [Madhav Marathe](#) and [Anil Kumar Vullikanti](#)

Mathematical and computational foundations of infectious disease epidemiology

SPEAKER: [Bryan Lewis](#)

ABSTRACT. As recent pandemics, such as the Zika and Ebola outbreaks have shown, diseases spread very fast in today's interconnected world, making public health an important research area. Some of the basic questions are: How can an outbreak be contained before it becomes an epidemic, and what disease surveillance strategies should be implemented? These are challenging problems at the interface of dynamical systems, graph theory, data mining, machine learning, high performance computing, theoretical computer science, economics and statistics. In this tutorial, we provide an overview of the state of the art in mathematical and computational epidemiology, which have typically not been studied from a multi-disciplinary perspective. The tutorial is suitable for both novice and expert researchers, and will be at a level that is accessible to most ICSB attendees who work in these areas.

08:30-12:00 Session 4F: Workshop: Developing Tutorials For Research Tools And Methods

CHAIR: [Alborz Bejnood](#)

LOCATION: Torgersen Hall - Room 3100

08:30 [Alborz Bejnood](#)

Workshop: Developing Tutorials For Research Tools And Methods
SPEAKER: [Alborz Bejnood](#)

ABSTRACT. Modern systems biology often requires an integrated computational and experimental approach. Countless tools and methods have been developed to facilitate research, but many lack engaging and approachable tutorials. This makes it more difficult for other scientists and students to learn how to use those tools in an effective way. Working through a specific comprehensive task that explicitly walks through acquiring relevant data, performing analysis, and visualizing results has been shown to be a more effective technique. In this workshop we will work through a series of modules we have developed to teach cancer systems biology, which have received positive student feedback, as a springboard and general template for creating tutorials of your own research tools and methods.

08:30-12:00 Session 4G: Workshop on Drug Response Measurement and Analysis

CHAIR: [Marc Hafner](#)

LOCATION: Torgersen Hall - Room 1020

08:30 [Marc Hafner](#), [Caitlin E Mills](#), [Adam C Palmer](#) and [Kartik Subramanian](#)

Workshop on Drug Response Measurement and Analysis

SPEAKER: [Marc Hafner](#)

ABSTRACT. Beyond the use of small molecule inhibitors as tool compounds to study a variety of biological processes, assays of cellular response to drugs are a fundamental aspect of the development and characterization of therapeutic molecules and the investigation of drug mechanism of action. However, drug response measurements and their analysis are not as trivial as one thinks and large-scale efforts across panels of cell lines have been plagued by inconsistencies. In addition, the quantification of drug combinations has been a topic of controversy for decades, with multiple methodologies leading to conflicting conclusions. These issues have motivated recent efforts to advance the methodology and theory for drug-response assays. In this workshop, we will present improved experimental and computational methods to generate reproducible dose-response measurements across cell lines, as well as theoretical approaches to quantify the sensitivity of cells to single drugs and drug combinations.

09:00-12:00 Session 5: StochSS: An Integrated Development Environment for Simulation and Analysis of Discrete Stochastic Biochemical Models

CHAIR: [Brian Drawert](#)

LOCATION: Torgersen Hall - Room 1040

09:00 [Brian Drawert](#), [Andreas Hellander](#), [Ben Bales](#) and
[Linda Petzold](#)

Tutorial on StochSS: An Integrated Development Environment for Simulation and Analysis of Discrete Stochastic Biochemical Models

SPEAKER: [Brian Drawert](#)

ABSTRACT. We present StochSS: Stochastic Simulation as-a-Service, an integrated development environment for modeling and simulation of deterministic and discrete stochastic biochemical systems. An easy to use WebUI enables researchers to quickly develop and simulate biological models on a desktop or laptop, which can then be expanded or combined to incorporate increasing levels of complexity. As the demand for computational power increases, StochSS is able to seamlessly scale by deploying cloud computing resources. The cloud computing facilities also make it possible to deploy StochSS as a multi-user software as-a-service (SaaS) environment with the capability to share and exchange models via a public model repository. StochSS currently supports simulation of ordinary differential equations and well-mixed discrete stochastic models, as well as parameter estimation of discrete stochastic models and efficient mesoscale simulation of spatial stochastic models. StochSS is available for download at www.StochSS.org.

13:30-16:30 Session 6: Monday Afternoon

CHAIR: [Young Cao](#)

LOCATION: Colonial Hall

13:30 [Lingchong You](#)

Programming bacteria in time and space

SPEAKER: [Lingchong You](#)

ABSTRACT. Microbes are by far the most dominant forms of life on earth. In every imaginable habitat, they form complex communities that carry out diverse functions. Microbial communities drive the geochemical cycling of diverse chemicals and through these activities shape the earth's climate and environment. They are also intimately tied to human physiology and health. Members of each microbial community may compete for resources, collaborate to process the resources or to cope with stress. They communicate with each other by producing and responding to signaling molecules. And they innovate by exchanging genetic materials. These interactions raise fundamental questions regarding the evolutionary and ecological forces that shape microbial consortia. Our lab has adopted a combination of quantitative biology and synthetic biology to explore these questions. We engineer gene circuits to program dynamics of one or more *Escherichia coli* bacterial populations and use them to examine questions in cellular signal

processing, evolution, ecology, and development. Analysis of these systems has provided insights into bacterial tolerance to antibiotics, developmental pattern formation and scaling, as well as strategies to use bacteria to fabricate functional materials by exploiting programmed self-organization.

14:00 [Yvonne Chen](#)

Engineering Next-Generation T Cells for Cancer Immunotherapy

SPEAKER: [Yvonne Chen](#)

ABSTRACT. The adoptive transfer of T cells expressing chimeric antigen receptors (CARs) has demonstrated clinical efficacy in the treatment of advanced cancers, with anti-CD19 CAR-T cells achieving up to 90% complete remission among patients with relapsed B-cell malignancies. However, challenges such as antigen escape and off-tumor toxicity limit the long-term efficacy and safety of adoptive T-cell therapy. Here, I will discuss the development of next-generation T cells that can perform Boolean logic signal processing to increase the robustness and specificity of therapeutic T cells. This presentation will highlight the potential of synthetic biology in generating novel mammalian cell systems with multifunctional outputs for therapeutic applications.

14:30 [Uwe Sauer](#)

Real-time metabolomics reveals the decision mechanism for cell division in *E. coli*

SPEAKER: [Uwe Sauer](#)

ABSTRACT. Our lab developed mass spectrometry-based methods to enable high-throughput metabolomics – enabling detection of 300-800 compounds in up to 2000 samples per day. These methods enabled, for example, mapping of the so far uncharted gene-metabolite associating network¹ or genome-wide discovery of novel enzyme activities². Since cellular metabolism responds directly and indirectly to environmental changes and regulatory events, changing metabolite concentrations are typically difficult to interpret. To delineate the different regulatory events in dynamic experiments, we recently developed near real-time metabolomics³. By following metabolome responses for minutes up to several hours at a resolution of a few seconds, this method allows to separate immediate kinetic and allosteric regulation from longer term processes. Here I will focus on so far unpublished results on the identification of the regulation processes that determine the decision to grow in *E. coli*. Specifically, we follow the metabolome responses during intermittent carbon feeding from non-growth supporting frequencies to growth. Surprisingly, even minute amounts of glucose gush through central metabolism all the way to building blocks of macromolecules. The decisive element for cell division

is the balance between synthesis and degradation of a single protein.

¹ Fuhrer T, Zampieri M, Sevin DC, **Sauer U** & N. Zamboni. 2017. Genome-wide landscape of gene-metabolome associations in *E. coli*. **Molecular Systems Biology** 13: 907.

³ Sevin DC, Fuhrer T, Zamboni N & U **Sauer U**. 2016. Nontargeted *in vitro* metabolomics for proteome-scale identification of novel enzymes in *E. coli*. **Nature Methods** 14:187-194.

³ Link H, Fuhrer T, Gerosa L, Zamboni N & **U. Sauer**. 2015. Real-time metabolome profiling reveals dynamics and regulation of the metabolic switch between starvation and growth. **Nature Methods** 12: 1091-1079.

15:00 [Coffee Break](#)

Coffee Break

SPEAKER: [Coffee Break](#)

15:30 [Julio Saez-Rodriguez](#)

Dynamic logic models complement machine learning to improve cancer treatment

SPEAKER: [Julio Saez-Rodriguez](#)

ABSTRACT. Large-scale genomic studies are providing unprecedented insights into the molecular basis of cancer, but it remains challenging to leverage this information for the development and application of therapies. We have performed an integrated analysis of the molecular profiles of large number of primary tumours and cancer cell lines, along with the response of the cell lines to anti-cancer compounds. Integration of this data with various sources of prior knowledge, in particular signaling pathways and transcription factors, points at molecular processes involved in resistance mechanisms. Our own analysis as well as the results of a crowdsourcing effort (DREAM challenge) reveals that prediction of drug efficacy is far from accurate, implying important limitations for personalised medicine. I will argue than an important aspect that needs to be further studied is the dynamics of signaling networks and how they response to drug treatment. I will show how applying logic models, trained with phosphoproteomic measurements upon perturbations, can further improve our understanding of the molecular basis of drug resistance, thereby providing new treatment opportunities not noticeable by an static molecular characterisation.

16:30-18:30 Session 7A: Parallel Session I a: Synthetic Biology

CHAIR: [Xueyang Feng](#)

LOCATION: Brush Mountain A & B

16:30 [Marian Breuer](#), [Clyde A. Hutchison III](#), [John I. Glass](#)

and [Zan Luthey-Schultheis](#)

The metabolic reconstruction of a minimal cell

SPEAKER: [Marian Breuer](#)

ABSTRACT. Establishing the core requirements of cellular life is an important challenge of biology. The question of the minimal set of biochemical functions necessary for a cell to grow and replicate has been studied from a number of angles for 20 years, culminating in the recent construction of the first "minimal cell" by synthetic biologists [1]: Starting from the pathogenic bacterium *Mycoplasma mycoides*, several cycles of genome design and assembly led to the removal of all genes not required for robust growth under optimal conditions. The resulting organism, Syn3.0, contains only 473 genes in a 531 kbp genome - less than any other known autonomously replicating cell. This minimal genome opens up the opportunity to, for the first time, understand all gene functions within a living cell - and cast them into a complete computational model encompassing all cellular functions.

As a first step towards this goal of a complete computational model of the minimal cell, we present here the metabolic reconstruction of Syn3.0, cast into a flux-balance analysis (FBA) model. Combining the genomic information of Syn3.0 with available experimental information on *Mycoplasma mycoides*, we have assembled a metabolic model encompassing around 150 genes. This model allows us to probe and analyze the metabolic properties of the minimal cell. In particular, it allows to rationalize experimental transposon insertion data [1] which suggests that disrupting some genes affects the cell not as strongly as disruption of other genes. Looking forward, the metabolic reconstruction will serve as a foundation for more comprehensive in silico models of Syn3.0, integrating all of its transcription, translation and metabolic processes.

[1] Hutchison C. A. et al. Science, 2016, 351, aad6253.

16:50 [Bert Huttan](#), [Jiayuan Sheng](#) and [Xueyang Feng](#)

A Synthetic Biosensor to Determine Peroxisomal Acetyl-CoA Concentration for Compartmentalized Metabolic Engineering.

SPEAKER: [Bert Huttan](#)

ABSTRACT. Sub-cellular compartmentalization is used by all eukaryotes and some prokaryotes as a means to create favorable microenvironments for various metabolic reactions. These compartments can concentrate enzymes, separate competing metabolic reactions, and isolate toxic intermediates in metabolic pathways. Such advantages have been recently

harnessed by metabolic engineers to improve the production of various high-value chemicals via compartmentalized metabolic engineering. However, one challenge in compartmentalized metabolic engineering is to determine key metabolite level in these compartments. Conventional techniques such as metabolomics analysis and transcription-based biosensors can only reflect cytosolic metabolite concentration instead of compartmental metabolite concentration. To this end, we developed a synthetic biosensor to determine a key metabolite, i.e., acetyl-CoA, in a representative compartment of yeast, i.e., peroxisome. This synthetic biosensor used highly efficient enzyme re-localization via PTS1 signal peptides to construct a metabolic pathway in the peroxisome, which solely converted peroxisomal acetyl-CoA to polyhydroxybutyrate (PHB) via three enzymes, phaA phaB and phaC. By quantifying the PHB level in yeast, we successfully determined peroxisomal acetyl-CoA level under various culture conditions. We next performed a proof of concept for our biosensor by screening a library of single knockout yeast mutants and identified one yeast mutant, Δ RPD3, which had elevated level of peroxisomal acetyl-CoA compared to wild type yeast. We expect our synthetic biosensors can be widely used to deepen our understanding of sub-cellular compartmental metabolism and facilitate the “design-build-test” cycle of compartmentalized metabolic engineering.

17:10 [Mojdeh Faraji](#) and [Eberhard Voit](#)

Compartmentalization of lignin biosynthesis using either phenylalanine or tyrosine in *Brachypodium distachyon*

SPEAKER: [Mojdeh Faraji](#)

ABSTRACT. In its efforts to produce economically feasible bioethanol from non-edible plant parts, the biofuel industry is interested in metabolically engineered biomass with reduced recalcitrance. Recalcitrance, the resistance of biomass to enzymatic degradation, limits the accessibility of enzymes to plant sugars and lowers the efficiency of ethanol fermentation. Recalcitrance is due to the heteropolymer lignin, which is interwoven with cellulose and hemicellulose in plant cell walls. Therefore, reducing lignin content and altering its composition in target plants is one of the primary goals of biofuel research. Interestingly, industries associated with textile production and the synthesis of organic compounds have identified lignin as a valuable starting compound for a novel processes and are interested in maximizing it. The branched structure of the lignin biosynthetic pathway exemplifies a nonlinear system whose functionality is difficult to understand without a computational modeling approach. We thus constructed a dynamic model of the pathway in the model grass *Brachypodium distachyon*, using ^{13}C -labeling data from control and perturbation experiments

for calibration. Unlike dicots, where phenylalanine is the sole precursor of monolignols, monocots like *Brachypodium* may use either phenylalanine or tyrosine, with the source affecting the ultimate monolignol composition. Although lignin synthesis has been studied for some time, the dynamics of the pathway is not entirely known, and the different monolignol compositions are puzzling. Preliminary analysis demonstrated that a single-compartment model could not explain the differences either. We thus formulated a dynamical model containing enzymes of the phenylalanine pathway at external surface of the ER and those of the tyrosine pathway in the cytosol. Intermediate metabolites are preferentially channeled within compartments but can be shuttled from one site to the other. With this design, the model results became consistent with experimental observations and can explain different monolignol compositions resulting from the preferential incorporation of either phenylalanine or tyrosine.

17:30 [Henning Redestig](#), [Moritz Beber](#), [Svetlana Galkina](#),
[Danny Dannaher](#), [Markus Herrgård](#) and [Nikolaus Sonnenschein](#)

Data-Driven Design of Cell Factories and Communities

SPEAKER: [Henning Redestig](#)

ABSTRACT. With ultra-precise genome editing tools at our disposal, the life sciences will shift from one-factor-at-a-time type of experiments to an ever increasing need to design complex non-intuitive manipulations involving simultaneous changes at multiple loci. In principle, integration of omics data and systems biology models would provide the means for optimizing knowledge gain through rational target selection and experimental design. They are not leveraged effectively, however, due to a lack of readily available tools to rapidly access and analyze public and private data to design genetic and experimental manipulations. With this project we aim to make a broad spectrum of omics data useful to biotechnology and life science research by integrating systems biology with design in a one-stop platform that will serve a variety of application areas, ranging from industrial biotechnology to agriculture and human health. A group of five academic partners (DTU, Chalmers, EMBL, EPFL and UMinho) will drive basic research on integrative, model-based omics data analysis to enable: (1) metagenomics-enabled design of novel enzymes and biochemical pathways, (2) omics data-driven design of cell factories for the production of chemicals and proteins, and (3) analysis and design of microbial communities relevant to human health, industrial biotechnology and agriculture. All research efforts will be integrated in an interactive, web-based platform available to both industrial and academic research. The platform will be composed of standardized and

interoperable components and therefore easily extensible. This will accelerate the process of bringing cutting edge systems biology research into practice. A first iteration of the platform, which features an intuitive user interface to data-constrained, genome-scale metabolic modeling that is based on interactive pathway visualizations, is already available at <http://dd-decaf.eu>.

17:50 [Snorre Sulheim](#), [Tjasa Kumelj](#), [Alexander Wentzel](#) and [Eivind Almaas](#)

Extended GEM of Streptomyces Coelicolor for production of secondary metabolites

SPEAKER: [Tjasa Kumelj](#)

ABSTRACT. People dying of infections that are not treatable anymore due resistance of pathogenic bacteria to various of antibiotics, have caused the urgent need to develop production of novel types of antibiotics. Streptomyces isolates are receiving considerable attention, especially due to unique antibiotic activity of their secondary metabolites. The genus Streptomyces is recognized to produce 40% of all known compounds with antibiotic activity, and it has been successfully used for heterologous expression.

The aim is to develop a mathematical and computational framework for the improvement of heterologous expression of gene clusters encoding for secondary metabolite pathways in Streptomyces coelicolor (*S.coelicolor*) strains. We have built a genome-scale metabolic model of *S.coelicolor* through extending the reaction universe of the existing iMK1208. The reaction universe has been extended by adding information from the previous iMA789 model. Additionally, the KEGG pathways have been used to add missing reactions and metabolites.

The resulting genome-scale metabolic model is then iteratively corrected and refined, according to internal consistency criteria and by comparing its predictions to experimental data, such as growth, gene-knockout, uptake and secretion rates. The resulting model is mapped to the KEGG namespace. This increase the value of the model, by simplifying further modifications and integration with the extensive pathway and reaction universe within the KEGG database.

18:10 [Yosef Roth](#) and [Jonathan Karr](#)

KineticDatanator: Tools for Aggregating Data for Biochemical Modeling

SPEAKER: [Yosef Roth](#)

ABSTRACT. Systems biology aims to understand how genotype influences phenotype. This requires comprehensive mechanistic models such as whole-cell models. Genomics has produced numerous datasets and predictors that could enable such models.

However, these resources are often overlooked because they are distributed across many databases and manuscripts. To accelerate whole-cell modeling, we are developing KineticDatanator, a tool for aggregating data for models from databases and predictors. KineticDatanator (a) retrieves data; (b) identifies relevant data for models from similar organisms, molecules, reactions, and conditions; (c) merges data to estimate model parameters; (d) reviews data; (e) organizes data for model construction; and (f) tracks provenance. KineticDatanator contains two layers: (a) a core for retrieving, filtering, merging, reviewing, and recording data and (b) modules which use this core to aggregate data from specific resources. KineticDatanator's core uses several tools to identify relevant data by chemical similarity (Open Babel), reaction similarity (E-zyme), species similarity (NCBI Taxonomy), and gene similarity (KEGG ORTHOLOGY). Currently, KineticDatanator includes modules for aggregating metabolite concentrations (ECMDB, YMDB), RNA concentrations (GEO), protein concentrations (literature), and kinetic parameters (SABIO-RK). Furthermore, KineticDatanator's modular architecture enables developers to contribute additional modules. We have used the SABIO-RK module to identify catalytic rate and affinity constants for 381 of 466 (82%) of the reconstructed metabolic reactions of *Mycoplasma pneumoniae*. 58% of the data was aggregated from Terrabacteria. 28% percent of the data was aggregated from observations of the identical reaction and 72% was aggregated from chemically-similar reactions. We plan to develop additional modules for additional data types such as promoter sites, protein localizations, DNA binding motifs, and RNA half-lives. Furthermore, we plan to develop a web-based interface to enable researchers to collaboratively aggregate data. We anticipate that KineticDatanator will accelerate whole-cell modeling and that these models will transform biological research.

16:30-18:30 Session 7B: Parallel Session I b: Cellular Signaling Networks I

CHAIR: [Silke Hauf](#)

LOCATION: Room 342 in Squires

16:30 [Sahand Jamal Rahi, Johannes Lärsch, Kresti Pecani, Alexander Y. Katsov, Nahal Mansouri, Krasimira Tsaneva-Atanasova, Eduardo D. Sontag and Fred R. Cross](#)

Oscillatory stimuli differentiate adapting circuit topologies

SPEAKER: [Sahand Jamal Rahi](#)

ABSTRACT. Biology emerges from interactions between molecules, which are challenging to elucidate with current techniques. An orthogonal approach is to probe for "response signatures" that identify specific circuit motifs, which describe interactions globally. For

example, bistability, hysteresis, or irreversibility are used to detect positive feedback loops. For adapting systems, which are ubiquitous in biology, such signatures are not known. Two different circuit motifs generate adaptation: negative feedback loops (NFLs) and incoherent feedforward loops (IFFLs), which specify different interactions and exhibit different biology. Based on exhaustive computational testing and mathematical proofs, we propose the first differential signatures: In response to oscillatory stimulation, NFLs but not IFFLs generically show i) 'refractory period stabilization' (robustness to changes in stimulus duration) or ii) 'period skipping'. Applying this approach to wild-type and mutant yeast, including a synthetic IFFL circuit, we identified the circuit dominating cell cycle timing. In *C. elegans* AWA olfactory sensory neurons, which are crucial for chemotaxis, we uncovered a Calcium-NFL leading to adaptation, difficult to find by other means, especially in wild-type, intact animals. These new response signatures allow direct access to the outlines of the wiring diagrams of adapting systems.

16:50 [Heidi Klumpe](#), [Yaron Antebi](#) and [Michael Elowitz](#)
Mapping BMP pairwise interactions describes how cells compute responses to BMP mixtures
SPEAKER: [Heidi Klumpe](#)

ABSTRACT. The BMP (bone morphogenetic protein) signaling pathway, critical in controlling diverse aspects of mammalian development, includes a dozen ligands and seven receptors that regulate a single biochemical output, the phosphorylation of Smad1/5/8 second messengers. Despite this seemingly redundant role for the BMP ligands, these ligands are not equivalent in all developmental contexts. Moreover, in the development of tissues including bone, heart, brain, and kidney, multiple BMP ligands are co-expressed. Indeed, it has been shown that ligand competition for shared receptors results in combinatorial signal processing. Specifically, cells do not respond to only the sum of two equivalent ligands, termed an "additive" response, but can be sensitive to the ratio of two inequivalent ligands, responding maximally to a balance, imbalance, or specific ratio of those ligands.

This framework provokes the general question of how the many BMP ligands combine with one another to control the activity of the BMP pathway. To address this question, we characterized the combinatorial properties of 14 BMP ligands by measuring responses to all possible 91 pairs. Using these data, we identify the distribution of integration modes, highlighting which BMP pairs combine additively and which pairs show a different, non-redundant behavior. Clustering the ligands based on their pairwise profile shows BMPs can be described in terms of equivalent groups. Within each cluster, ligands combine additively, while members of distinct clusters are integrated using a

specific pairwise mode as previously described. Furthermore, mathematical models of BMP signaling indicate that receptor abundance can alter signal integration by modulating competition for ligand binding sites. Starting from this theoretical prediction, we show experimentally how changes in receptor profile alter the functionally equivalent clusters of BMP signals. These results should provide a more predictive understanding of how cells communicate using combinations of ligands and changes in receptor profile.

17:10 [Bhanwar Lal Puniya](#), [Robert Todd](#) and [Tomas Helikar](#)

Systems modeling of interplay among extracellular cytokines regulating phenotypic plasticity of CD4+ T-cell differentiation

SPEAKER: [Bhanwar Lal Puniya](#)

ABSTRACT. T cells provide cell mediated immunity in vertebrates against pathogens and diseases. During an immune response, naive CD4+ T cells activate and differentiate into effector or regulatory cell sub-types. Recent studies have shown that T-cell phenotypes exhibit plasticity that involves production of intermediate states, e.g., phenotypes co-expressing lineage specific transcription factors, and interconversion between previously thought terminally differentiated phenotypes, e.g., Th17 to Th1. The plasticity of T cell differentiation is regulated by cytokine microenvironment, intracellular signaling, and gene regulation, but the exact mechanism is unclear. Dynamic interplay of extracellular cytokines play an important role in regulation of CD4+ T cell differentiation plasticity. Recently, computational modeling emerged as an important tool to study the dynamics of biological systems, therefore can be used to gain insight into regulation of T-cell differentiation plasticity. We have developed a comprehensive logic-based computational model depicting regulatory mechanisms involved in CD4+ T cell differentiation. We obtained information of regulation of CD4+ T cell differentiation from literature and constructed the model in Cell Collective. The model consists of four master transcription factor regulators i.e. Tbet, GATA3, RORgt, and Foxp3, six STATs and other signaling molecules. The model incorporates 96 regulatory interactions among 38 components that include nine cytokines in extracellular environments. The model was simulated under 510 combinations of nine extracellular cytokines (environmental conditions). Each environmental condition was characterized by varying doses of active cytokines. Simulation and analysis results suggest ten potentially stable phenotypes, including four main types of differentiated CD4+ T cells, as well as hybrid phenotypes co-expressing lineage specific master regulators. In addition to already known phenotypes, we found novel phenotypes co-expressing lineage specific transcription factors. In conclusion, we predicted the optimal activity levels of extracellular

cytokines that induce the production of novel CD4+ T cell phenotypes co-expressing lineage specific transcription factors.

17:30 [Alberto Giaretta](#), [Gianna Maria Toffolo](#) and [Timothy Charles Elston](#)

Stochastic model of HPV early promoter predicts bursts like pattern of gene expression

SPEAKER: [Alberto Giaretta](#)

ABSTRACT. High risk forms, human papillomaviruses (HPV) early promoter regulation is of paramount importance to understand the early phase of the infection and cancer evolution. The aim of this work is to develop a novel stochastic mathematical modeling framework, able to capture known biological mechanisms related to HPV early promoter regulation. The model includes modules designed to account for the transcriptional, post-transcriptional and translational regulation of E1, E2 early genes and E6 and E7 oncogenes, properly coupled to form the entire network. To appropriately model the post-transcriptional regulation, the major splicing sites and the splicing factor SRSF1 regulation were considered. The Master Equation governing the model stochastic evolution was solved by means of the Gillespie algorithm and the stochastic behaviour was compared with the deterministic mean system behavior provided by a quasi-equilibrium approximation of the Master Equation. The model resulted to be able to fit a dataset with early promoter activities and to reproduce patterns qualitatively/quantitatively consistent with the known biology of the virus. Results also suggested that stochasticity plays a pivotal role in determining the dynamics of HPV gene expression. In particular, the combination of positive and negative feedback regulation of the early promoter generates stochastic bursts of gene expression, having amplitude and frequency modulated by, respectively, the relative strengths of the feedback loops and the post-transcriptional regulation by splicing. This latter mechanism is also responsible for a stochastic switch behavior that moves the system from normal infection to a condition in which E6 and E7 are overexpressed while E1 and E2 are no longer transcribed, consistent with HPV integration. The developed model appears as an important tool in predicting the early promoter regulation, useful to shed light in important and still elusive mechanisms and showing the pivotal importance of the intrinsic stochasticity in the HPV gene expression.

17:50 [Simon Mitchell](#), [Koushik Roy](#), [Thomas Zangle](#) and [Alexander Hoffmann](#)

Identifying non-genetic origins of cell-to-cell variability in B-lymphocyte proliferation through systems biology

SPEAKER: [Simon Mitchell](#)

ABSTRACT. The proliferation of B lymphocytes to enable production of antibodies specific to invading pathogens is critical for an effective immune response. The prevailing hypothesis that B-cell fate decision-making is highly stochastic was based on timepoint measurements revealing high generational heterogeneity and probabilistic mathematical models that recapitulated population dynamics. Here, using multi-scale mechanistic computational modeling of the molecular network that is responsible for cellular decision making, and live cell microscopy of B-cell population expansion, we are able to quantify the contributions of both founder cell heterogeneity (extrinsic noise) and molecular stochasticity (intrinsic noise). Indeed, we identify non-genetic heterogeneity in founder cells as the key determinant of B-cell population dynamics, rather than probabilistic decision making. This means that contrary to previous models only a minority of genetically identical founder cells contribute the majority to the population response. We computationally identify, and experimentally confirm, non-genetic determinants of proliferative outcome. Our finding of the largely deterministic nature of B-lymphocyte responses renders the control of humoral immune responses more amenable to diagnostic and therapeutic development than previously thought.

18:10 [Chu Chen](#), [Ian Whitney](#), [Anand Banerjee](#), [Palak Sekhri](#),
[David Kern](#), [Adrienne Fontan](#), [John Tyson](#), [Iain Cheeseman](#) and [Ajit Joglekar](#)

The biochemical design of the mitotic checkpoint

SPEAKER: [Ajit Joglekar](#)

ABSTRACT. Accurate chromosome segregation during mitosis requires that the sister kinetochores on each chromosome are stably attached to spindle microtubules prior to cell division. If one or more kinetochores are unattached, they delay cell division by activating the mitotic checkpoint, also known as the Spindle Assembly Checkpoint (SAC). The SAC is a complex signaling cascade uses many kinetochore proteins, signaling proteins, and their extensive phosphoregulation, to produce a diffusible ‘wait-anaphase’ signal. The objectives of the SAC cascade are two-fold: to maximize accurate chromosome segregation and to minimize mitotic delays. For the first objective, it is essential that a single unattached kinetochore generates a strong signal to delay anaphase onset. To meet the second objective, the large number of unattached cells present at the beginning of mitosis should not produce a proportionately large signal. How a nanoscopic kinetochore can generate a strong ‘wait-anaphase’ signal to inhibit anaphase over a 106-fold larger cellular volume, or why larger numbers of unattached kinetochores don’t produce a proportionately larger signal remain two fundamental questions in cell biology. The primary obstacle to answering these questions has been the localization of most of the

signaling reactions within the nanoscopic kinetochore. Therefore, we engineered the ‘eSAC’ – a diffusible, kinetochore-independent, and quantifiable SAC activator. The eSAC ectopically activates the SAC by conditionally dimerizing the scaffold protein for SAC signaling with the kinase that activates the cascade. Using the eSAC, we conducted quantitative dose-response analyses of the SAC cascade in live cells. These analyses reveal two novel properties of the SAC cascade. We find that the recruitment of multiple SAC proteins by the signaling scaffold stimulates synergistic signaling. This enables a small number of scaffold molecules produce a disproportionately strong anaphase-inhibitory signal. However, many scaffold molecules signal concurrently, they compete for a limited cellular pool of SAC proteins. This frustrates synergistic signaling and modulates signal output. We propose that these two mechanisms institute automatic gain control – inverse, non-linear scaling between the signal output per kinetochore and the unattached kinetochore number, and thus achieve the two objectives of SAC signaling.

16:30-18:30 Session 7C: Parallel Session I c: Omics Technol & Application

CHAIR: [Jing Chen](#)

LOCATION: Colonial Hall

16:30 [Akinori Nishi](#), [Katsuya Ohbuchi](#), [Hirotaka Kushida](#),
[Takashi Matsumoto](#), [Keiko Lee](#), [Haruo Kuroki](#), [Shigeki Nabeshima](#), [Kazuhiro Hanazaki](#), [Chika Shimobori](#),
[Nagisa Komokata](#), [Hitomi Kanno](#), [Naoko Tsuchiya](#),
[Makoto Zushi](#), [Ayako Yachie](#), [Yukiko Matsuoka](#), [Hiroaki Kitano](#) and [Masahiro Yamamoto](#)

**Systems Biology of Herbal Medicine:
Pharmacological property of complex herbal formulation**

SPEAKER: [Akinori Nishi](#)

ABSTRACT. Traditional herbal medicine (THM) consists of multiple herbal ingredients, and the combination of these herbs is regarded as the key to their pharmacological efficacy. For example, maoto, a traditional Japanese medicine (Kampo) that is prescribed for influenza-like symptoms, contains four different herbs: Armeniacae Semen (AS), Glycyrrhizae Radix (GR), Cinnamomi Cortex (CC), and Ephedrae Herba (EH). While the effect of the major active ingredient “ephedrine” (from EH) has been well studied, the pharmacological action of maoto as a whole remedy remains unknown. In our previous study, seven major ingredients were derived from the constituent herbs and several hundred ingredients/metabolites were detected in rat plasma after maoto administration. This indicates that the pharmacological properties of maoto result from a complicated combination of multiple ingredients that may not be attributable to EH alone. To elucidate the combinatorial effect of maoto

further, we compared pharmacological, metabolomic and transcriptomics properties among ephedrine, a mixture of major ingredients (toy-maoto) and maoto in a rat model of polyI:C-induced inflammation. Maoto ameliorated both disease symptoms and the surge in proinflammatory cytokines. Although ephedrine contributed largely to suppressing the acute cytokine surge, the inhibition of body weight loss caused by the mixture of herbs was not reproduced by ephedrine alone. In the plasma metabolome, maoto broadly affected lipid mediator responses and modulated the balance of proinflammatory and anti-inflammatory lipid mediators. By contrast, ephedrine played a major role in the early effects of maoto, including alteration of amino acids and metabolites related to the TCA cycle. In the lung transcriptome, ephedrine inhibited major proinflammatory factors, while toy-maoto and maoto affected broader pathways. In summary, we have demonstrated that the specific pharmacological properties of THM are exerted by a mixture of herbs but not by a single ingredient via the horizontal integration of pharmacological and molecular profiling.

16:50 [Iulia M. Lazar](#), [Ina Hoeschele](#) and [Shreya Ahuja](#)
Cell Cycle Model System for the Identification of Molecular Markers of Cancer
SPEAKER: [Iulia M. Lazar](#)

ABSTRACT. With the advent of high-throughput technologies capable of delivering massive amounts of data, the demand for comprehensive panels of molecular markers of disease has increased correspondingly. Comprehensive panels that stem from whole-genome expression, transcriptome or other omics profiles (proteome, secretome, exosome, glycome, metabolome) are sought for every level of diagnostics, from preliminary screening for the presence or risk of a disease, to staging, response to treatment, progression or relapse. In this work, we explored the outcome of mass spectrometry (MS)-based proteomic experiments aimed at profiling the G1 and S cell cycle stages of cancer and nontumorigenic cells to identify functionally-related biomarker proteins that could be recommended for further exploration in clinical context.

The MCF7/ER+, SKBR3/HER2+ breast cancer and MCF10 non-tumorigenic cells were used as an experimental model system. Protein extracts from each cell line and cell cycle stage were analyzed by nano-LC-MS/MS, and the raw data were processed with the Discoverer and Mascot search engines. Each cell state enabled the identification of a substantial number of markers, totaling ~350 proteins with biomarker potential. Cluster analysis revealed that the top enriched biological processes that were represented by these proteins included three major categories related to DNA damage repair, oxidative stress and signaling, as well as several smaller categories pertaining to

epithelial to mesenchymal transition, adhesion, response to various types of radiation, and regulation of cell proliferation and apoptosis. A number of proto-oncogenes and mutated proteins were identified, as well. To understand the power and challenges associated with the use of proteomic data in biomarker research, we will detail in our presentation the experimental design, the mass spectrometric and statistical protocols used for protein identification and validation, and the bioinformatics work-flow that was developed for data interpretation. The role of protein-protein interactions and gene regulatory networks in the development of biomarker signatures characteristic of a disease will be discussed, and the impact of driver mutations on aberrant cell cycle progression and cell proliferation will be addressed.

17:10 [Ghofran Othoum](#), [Magbubah Essack](#), [Salim Bougouffa](#), [Rozaimi B. Mohamad Razali](#), [Ameerah Bokhari](#), [Soha Alamoudi](#), [Maged M Saad](#), [Feras F. Lafi](#), [Andre Antunes](#), [Heribert Hirt](#) and [Vladimir B. Bajic](#)

Genome mining of *Bacillus licheniformis* strains from the Red Sea with focus on the biosynthesis of antimicrobial products

SPEAKER: [Ghofran Othoum](#)

ABSTRACT. *B. licheniformis* has been successfully identified and deployed as an active producer of a number of industrially relevant products including surfactants and antibiotics. Furthermore, *B. licheniformis*' ability to form spores makes it a potential candidate to be used as a biological control agent. Here, we report the complete genome sequences of two *B. licheniformis* strains Bac48 and Bac84 that were isolated from mangrove mud and microbial mat from Rabigh lagoon by the Red Sea. Using the 16S rRNA gene, Bac48 and Bac84 are 99% and 98% similar to *B. licheniformis* DSM 13, respectively. We utilize genome mining approaches to show how the genomes of these strains harbor more non-ribosomally synthesized peptide (NRP) clusters compared with other publically available *B. licheniformis* strains with complete genome sequences. Specifically, two NRP clusters are detected only in Bac48 and Bac84 with 52 and 46 genes respectively. The clusters are predicted to produce Fengycin with an average cumulative blast score of 31586 and Bacitracin with an average cumulative blast score of 45477 against the Minimum Information about a Biosynthetic Gene cluster database (MIBiG). We accordingly hypothesize that Bac48 and Bac84, two Red Sea strains, are good candidates to be used as microbial chassis for antimicrobial production especially lipopeptides.

17:30 [Yin Hoon Chew](#), [Arthur Goldberg](#) and [Jonathan Karr](#)
Toward A Whole-Cell Model of H1 Human Embryonic Stem Cells (hESCs): A Genome-Scale Metabolic Model

SPEAKER: [Yin Hoon Chew](#)

ABSTRACT. Stem cell behaviors such as self-renewal and differentiation result from complex interactions among signaling, gene regulation, metabolism, and other pathways. Extensive research has elucidated many details of these pathways. However, we do not have a predictive understanding of how these pathways collectively determine behavior. To gain an integrated understanding of stem cells, we are developing a whole-cell computational model of the relatively well-characterized H1 hESC line.

Our model will be composed of multiple submodels of individual pathways such as signaling, gene regulation, and metabolism. The model will be based on a wide range of genomic and biochemical data. (1) We constructed an H1 genome by mapping published H1 WGS reads onto the hg19 reference. This genome will provide the foundation for the genes and reactions represented by the model. (2) We developed a metabolism submodel by (a) reconstructing the cell and media composition, protein expression, kinetic parameters, reaction fluxes, and growth rate of H1 hESCs; (b) constructing a seed network from the Recon 2.2 consensus model based on the reconstructed proteome; (c) parsimoniously add additional reactions from Recon 2.2 using CORDA2 until the network could produce each reconstructed cell component; (d) bounding the reaction fluxes by Michaelis-Menten rate laws; and (e) calibrating the submodel using the reconstructed cell composition, reaction fluxes, and growth rate. (3) We plan to (a) create submodels of signaling, gene regulation, RNA and protein synthesis and degradation, replication, and cell division; (b) expand the metabolic submodel with missing reactions that produce the metabolites required in other submodels; (c) integrate all submodels; and (d) validate the integrated model by comparison to observed hESC phenotypes such as its short G1 phase and rapid growth.

Ultimately, we aim to use the model to help elucidate the mechanisms of stem cell behaviors and help engineer stem cells for regenerative medicine.

17:50 [Sandeep Kaur, Jenny Vuong and Sean O'Donoghue](#)

A strategy for modelling and visualising phosphoproteomic datasets

SPEAKER: [Sandeep Kaur](#)

ABSTRACT. An increase in the number of phosphoproteomic datasets obtained via high-throughput mass-spectrometric methods incites the need for tools that enable exploring them.

Minardo is a strategy to enable exploration of time-series phosphoproteomic dataset in terms of the corresponding kinases and phosphatases for observed

phosphorylation alterations, overlaid on a cellular topology and depicted with time. The Minardo strategy has been successfully applied, by manually putting together the knowledge, to two high-throughput phosphoproteomic datasets. Here, we present work towards automation of Minardo, constructed as a web based tool.

The network identification methods (i.e. determining the involved kinases and phosphatase) combine multiple data-sources containing exact phosphatases and kinases for any given site (e.g. PhosphositePlus and DEPOD) as well as resources that allow us to hypothesise the possible enzymes that may be involved (such as BioGrid and Gene Ontology Annotations). Localisation datasets (such as Compartments) are also utilised to hypothesise the location of the occurrence of the phosphorylation or dephosphorylation reaction.

We provide an evaluation of the results obtained via our automated methods, for the two phosphoproteomic datasets, against their manually annotated versions. We observe good precision and poor recall for the kinase and phosphatase annotations, with phosphatase annotations having much worse recall.

These works represent a starting point for building tools for exploring phosphoproteomic datasets in the context of networks representing reactions at the level of sites. Our evaluation results of good precision and poor recall reflect on the current status of knowledge in existence for phosphorylation sites. We also provide a discussion of complementary methods, as well as future directions.

18:10 [Linda Krause](#), [Fabian J. Theis](#), [Nikola S. Mueller](#) and [Stefanie Eyerich](#)

Multi-omics analysis of T helper 22 cells

SPEAKER: [Linda Krause](#)

ABSTRACT. T helper (Th) 22 cells represent the newest member of the T helper family. As part of adaptive immunity, the physiological role of Th22 cells is to maintain the integrity of epidermal barriers. However, if this per se positive function is outbalanced it can turn pathologic and lead to deviations in the skin like they are seen in e.g. psoriasis. Aim of this project is to comprehensively characterize the Th22 phenotype and to identify similarities, differences and possible relationships to other known T helper subsets. To achieve this aim, we analyzed in total 60 T cell clones from different subsets derived from human biopsies or blood of chronic inflammatory skin diseases on protein and mRNA level by using Bioplex assays and whole transcriptome expression arrays, respectively, in a matched analysis setting. By using a combination of six clustering methods, the clones were grouped into subsets based on their cytokine secretion profile

delivering several Th22 clones but also all other known Th subsets. These identified clusters were then compared using the transcriptomics data to describe similarities and differences of Th22 cells to other subsets. To obtain candidate genes, we fit several regularized logistic regressions (elastic net penalty) with the subset membership as outcome and all measured mRNA transcript as explanatory variables. We controlled the false discovery rate of the resulting candidate genes using stability selection. We found at least six genes, which are unique for the Th22 phenotype. Investigating the shared features revealed a higher similarity between Th22 and Th17 cells as compared to the other subsets. The selected genes are currently verified on the epigenetic level using DNA methylation data as well as experimentally for their role in Th22 differentiation. Specific targeting of Th22 cells by the identified genes may be useful to equilibrate outbalanced immune responses in human diseases.

18:30-20:30 Session 8: Welcome Reception and a Keynote Speech

CHAIR: [John Tyson](#)

LOCATION: Old Dominion Ballroom

18:30 [Organizers](#)

Welcome

SPEAKER: [Organizers](#)

18:45 [Xiaoliang Sunney Xie](#)

Single-Cell Genomics: When Stochasticity Meets Precision

SPEAKER: [Xiaoliang Sunney Xie](#)

ABSTRACT. DNA exists as single molecules in individual cells. Consequently, gene expression is stochastic. We have recently developed a method for single cell transcriptome with high detection efficiency and accuracy, revealing intrinsic correlations among different genes, which has previously been masked within the stochastic noise. For a particular human cell type, we were able to extract ~120 transcriptionally correlated modules acting from the stochastic gene expression data of ~700 individual cells under a non-equilibrium steady state condition.

The fact that there are 46 different individual DNA molecules (chromosomes) in a human cell dictates that genomic variations occur stochastically and cannot be synchronized among individual cells. Probing such genomic variations requires single-cell and single-molecule measurements. However, existing whole-genome amplification (WGA) methods are limited by low accuracy of copy-number variation (CNV) detection and low amplification fidelity. We have developed transposase-based methods for single cell whole genome amplification, which have superseded previous methods. With the improved genome coverage, we developed a high resolution single cell chromatin

conformation capture method, which allows for the first 3D genome map of a human diploid cell. Applications and implications to biology and medicine of these new approaches will be discussed.

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PROGRAM FOR TUESDAY, AUGUST 8TH

Days: [← previous day](#) [next day →](#) [all days ↕](#)

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08:00-17:00 Session : Registration

LOCATION: Williamsburg Room

08:30-10:30 Session 9: Tuesday Morning

CHAIR: [Daniel Gallahan](#)

LOCATION: Colonial Hall

08:30 [Kevin Janes](#)

Stochastic frequency matching of incompletely penetrant onco-phenotypes

SPEAKER: [Kevin Janes](#)

ABSTRACT. Perturbation of cancer cells often leads to heterogeneous outcomes, in that most cells exhibit a dominant phenotype, but the rest appear resistant or hypersensitive to the perturbation. If the penetrance of such a phenotype is heritably incomplete, then it becomes extremely difficult to decipher the upstream molecular events that heterogenize the population and cause response variability. By combining quantitative measurements with dynamical models, systems approaches should be useful if provided with a core network of important biomolecules. The daunting hurdle lies in identifying phenotype-relevant regulatory heterogeneities that define the network for penetrance at the single-cell level. Here, I will introduce a new approach, called stochastic frequency matching (SFM), for elaborating the molecular networks upstream of incompletely penetrant phenotypes. SFM identifies and parameterizes single-cell heterogeneities—which emerge after a uniform perturbation but before the appearance of a variable phenotype—to hone in on regulatory states corresponding to future penetrance. For an onco-phenotype incompletely triggered by ErbB receptor tyrosine kinase signaling in 3D cultured breast epithelia, we implemented SFM using microarrays to uncover a network of critical nucleocytoplasmic regulators.

09:00 [Sylvia Plevritis](#)

Optimizing drug combinations using single-cell perturbation response to account for intratumoral heterogeneity

SPEAKER: [Sylvia Plevritis](#)

ABSTRACT. An individual tumor is composed of a heterogeneous collection of single cells with distinct molecular and phenotypic features, a phenomenon termed intratumoral heterogeneity. Intratumoral heterogeneity poses serious challenges to cancer treatment, motivating the need for combination therapies. We optimize drug combination by accounting for intratumoral heterogeneity through the analysis of single cell signaling perturbations when an individual tumor sample is screened by a drug panel. Mass Cytometry Time-of-Flight (CyTOF) is a high throughput single cell technology that enables the simultaneous measurements of multiple (>40) intracellular and surface markers at the level of single cells for hundreds of thousands of cells in a sample, analyzed pre- and post-treatment. We developed a computational framework, entitled DRUG-NEM, to analyze CyTOF-based single cell drug perturbation data for the purpose of individualizing drug combinations. In its current implementation, DRUG-NEM optimizes the drug combinations by choosing the minimum number of drugs that produces the maximal desired intercellular effects based on nested-effects modeling. We demonstrate the performance of DRUG-NEM for leveraging single cell perturbation data to identify optimal drug combinations on tumor cell lines and primary leukemia samples.

09:30 [Coffee Break](#)

Tuesday Morning Coffee Break

SPEAKER: [Coffee Break](#)

10:00 [Andre Levchenko](#)

Systems analysis of invasive cancer spread: from the bench to bedside

SPEAKER: [Andre Levchenko](#)

10:30-12:30 Session 10A: Parallel Session II a: Multicellular Systems Biology

CHAIR: [Jianhua Xing](#)

LOCATION: Brush Mountain A & B

10:30 [Brian Ji](#) and [Dennis Vitkup](#)

Ecological Dynamics of Gut Microbiota

SPEAKER: [Brian Ji](#)

ABSTRACT. The gut microbiome is now widely recognized as a dynamic ecosystem that plays an essential role in health and disease. While current sequencing technologies make it possible to estimate relative abundances of host-associated microbiota over time, the processes governing their temporal dynamics remain poorly understood due to significant bacterial diversity and interaction complexity in the gut. Consequently, as in other ecological systems, it is important to investigate global statistical relationships that describe microbiota dynamics. Here we perform

such an ecological analysis using several high-resolution time series data sets from humans and mice, finding that microbiota dynamics can be described by robust scaling relationships spanning several orders of magnitude. Specifically, we observe power laws governing changes in population abundance, species local residence times, and mean versus variance scaling of individual taxa abundances over time. Interestingly, the observed patterns are highly similar to those describing multiple other ecological communities and economic systems, including temporal fluctuations of animal populations and performance of publicly traded companies. We find that these scaling relationships are altered in mice receiving different diets, and identify individual taxa whose dynamics deviate from overall trends in each group. Collectively, our results provide a systematic statistical framework for understanding complex ecological processes in the gut microbiome.

10:50 [Xiao-Jun Tian](#), [Dong Zhou](#), [Youhua Liu](#) and [Jianhua Xing](#)

The Transition from Acute Kidney Injury to Chronic Kidney Diseases Comes from Evolutionary Compromise

SPEAKER: [Xiao-Jun Tian](#)

ABSTRACT. Acute kidney injury (AKI) is associated with a high risk of death. The death rate from AKI is much higher than that from prostate cancer, breast cancer, heart failure, diabetes. In response to renal injury, a complex wound-healing program is triggered to minimize the damage. If the damage is small, the function of the kidney is completely recovered. However, severe AKI or repeated episodes of AKI leads to kidney fibrosis and Chronic kidney disease (CKD). Interestingly, the long-term outcome of AKI patients after discharge from the hospital varies from person to person. While some of them are completely recovered from AKI, the others progress to fibrosis. However, the underlying mechanism is not fully understood.

Here, we first built a cell-cell communication mathematic model for renal homeostasis and fibrosis in response to injury. We found that depending on the level of injury, the outcomes can be death, perfective-adaptive AKI, imperfective-adaptive AKI, and maladaptive CKD. We verified this prediction in mice with different duration of ischemia-reperfusion injury (IRI) treatment. Furthermore, we demonstrated computationally and experimentally that imperfective adaptive AKI has a double-edge effect for the subsequent injury and significant increase the risk of fibrosis. On one hand, that imperfective adaptive AKI functions as a priming factor to reduce the death risk. On the other hand, it increases the fibrosis risk. Using combined mathematical modeling and mouse model

studies, we not only recapitulates multiple-objective optimization of the renal system but also elucidates lots of seemly controversial experimental results. Most importantly, we proposed and tested a new treatment design by targeting on the dynamics of the Wnt signaling which can both reduce the death and fibrosis risk, especially under the circumstance of severe renal damage.

11:10 [Lucas van der Zee](#), [Thierry Mondeel](#), [Hans Westerhoff](#) and [Matteo Barberis](#)

DECIPHERING CELL CYCLE ROBUSTNESS BY A MULTI-SCALE FRAMEWORK INTEGRATING CELL CYCLE AND METABOLISM IN BUDDING YEAST

SPEAKER: [Matteo Barberis](#)

ABSTRACT. Cell cycle and metabolism are coupled networks. For example, cell growth and division require synthesis of macromolecules which is dependent on metabolic cues. Conversely, metabolites involved in nucleotide and protein synthesis are fluctuating periodically as a function of cell cycle progression. Although computational models of these networks are being developed for some time, to date no effort has been made to integrate these two systems in any organism. We aim to investigate cell cycle robustness by generating the first multi-scale model that integrates cell cycle with metabolism, and investigating their bidirectional regulation. Connections among these two biochemical networks have been recently elucidated in budding yeast. However, high-throughput and manually curated studies point at many more physical interaction, which relevance for precise cell cycle timing remains unknown. A framework is presented that integrates a Boolean cell cycle model with a constraint-based model of metabolism, incorporating mechanistic and high-throughput interactions. Directionality and effect are incorporated for the mechanistic interactions. Conversely, as this information is unknown for the high-throughput interactions, an informed optimization algorithm has been developed to generate models that can incorporate it iteratively. To verify the results of the informed optimization algorithm against metabolomic data, changes in flux through a number of metabolic pathways are compared to metabolic pathway enrichment time-series. The multi-scale model predicts expected changes in a number of pathways, ranging from amino-acid to pentose phosphate to lipid metabolism. Many model variants that differ in number and directionality of interactions robustly predict the effect of definite cell cycle-metabolism pairs. Furthermore, the integrative model shows a temporal export of acetate, pyruvate and alanine, reminiscent of yeast metabolic oscillations. Altogether, our multi-scale framework is able to integrate computer models of biological networks with high-

throughput data, to capture the functional connectivity among their elements that ultimately results in systems robustness.

11:30 [Samantha Herath, Mark Ebeid](#) and [Daniel Lobo](#)

Automatic Inference of Dynamic Regulatory Networks Controlling Shape And Form

SPEAKER: [Daniel Lobo](#)

ABSTRACT. Multicellular biological organisms possess the extraordinary ability to grow and maintain intricate body shapes and forms. However, the processes regulating the growth of exact shapes in a developing organism are not well understood due to the non-linearity of gene regulatory networks and the complex, systemic interactions between tissue and regulatory signals. It is now clear that robust mathematical approaches combined with automated reverse-engineering methods are necessary to describe, infer, and understand these dynamic processes controlling tissue growth and shape formation. To this end, we have developed a mathematical framework based on continuous dynamics and a machine learning methodology based on evolutionary computation to accurately reverse-engineer and predict the growth and regulation of multicellular biological forms and shapes. Our formulation is based on diffusion-advection-reaction partial differential equations, permitting the fast and efficient simulation of multicellular growth. In a continuous fashion, this mathematical framework models the proliferation of cells, their chemotactic migrations, and the adhesive forces between them, in addition to the genetic regulatory mechanisms controlling these processes. Importantly, our computational methodology can automatically infer de novo these complex dynamic models directly from quantitative experimental data, including the precise genes, their interactions, and model parameters necessary and sufficient to develop and maintain specific biological forms and shapes. As a proof of concept, we have applied our novel framework to infer the genetic network controlling the allometric growth in regenerating planarian worms. Using a dataset of planarian experiments and their resultant morphologies, we have discovered a suitable, dynamic genetic model that accurately recapitulates the regeneration of shape and form after surgical amputations. This work paves the way for the understanding and reverse engineering directly from experimental data the dynamic regulation of biological shapes, an essential step towards the much sought-after quantitative and predictive models in developmental and regenerative biology.

11:50 [Manish Kumar, Boyang Ji, Parizad Babaei](#) and [Jens Nielsen](#)

A systems biology approach to understand the association between gut microbiota and malnutrition

SPEAKER: Manish Kumar

ABSTRACT. Malnutrition in children of low-income countries is severe health concern. Recently, some 16S rRNA and metagenomic (whole genomic DNA fragments) sequencing based studies demonstrated the association between gut microbiome and malnutrition. In this work, we have used a systems biology approach, namely genome scale metabolic modeling (GEM), to understand the metabolic variations in gut microbiome during health and malnutrition. We have generated GEMs of 58 most abundant gut bacteria from the healthy (Swedish, Bangladeshi, and Malawian) and malnourished children (Bangladeshi and Malawian). These species represent five phyla, viz. Firmicutes (61.8%), Bacteroidetes (17.6%), Actinobacteria (10.3%), Proteobacteria (8.8%), and Fusobacteria (1.5%). Single species GEMs were simulated to predict the metabolic capabilities of most abundant part of gut microbiota in the term of synthesis of beneficial small molecules, such as short chain fatty acids and amino acids. Results suggested that the gut microbiota in Bangladeshi and Malawian children is significantly less diverse than Swedish children in the term of metabolic capabilities. There is only a slight difference in production of SCFAs and AAs between healthy and malnourished Bangladeshi children. For Malawian children there seems to be no metabolic difference between healthy and malnourished children, which could point to an effect of vitamins and/or minerals. These results indicate that metabolic potential of gut microbiome significantly differs between children, more susceptible to malnutrition (Bangladeshi and Malawian) and children, insusceptible or less susceptible to malnutrition (Swedish). Gut bacteria GEMs also allowed to perform community-level analysis using mixed-bag modeling (merged multi-species models) and pairwise interactions between species. Similarly, this analysis highlighted the differences in gut microbiome between more and less susceptible children groups in the term of metabolic potential as well as interaction patterns among the species in silico microbial communities.

10:30-12:30 Session 10B: Parallel Session II b: Cancer Systems Biology I

CHAIR: Shannon Hughes

LOCATION: Room 342 in Squires

10:30 Dirk Fey, David R Croucher, Axel Kuehn, Laura Tuffery, Melinda Halasz, Walter Kolch and Boris N Kholodenko

Patient-specific modelling and cell-to-cell

variability of the JNK-p53 activation dynamics in primary and relapsed tumours.

SPEAKER: [Dirk Fey](#)

ABSTRACT. In cancer, nearly all aspects of cancer pathophysiology, including cancer initiation, development, progression and metastasis are driven by the dysregulation of one or more signalling networks. These signalling networks consist of sets of genes that are dynamically organised. In response to a perturbation the activity of the network changes over time. In this way, signalling pathways exert finely tuned control over cell fate decisions that ultimately determine the behaviour of cancer cells. However, we barely understand how these dynamic activation patterns are shaped by differences between cells and patients: How does cell-to-cell variability affect drug responses? How does the genomic background of patients affect the network's input/output behaviour? Here, I will address these questions focusing on the on the dynamic network around the JNK and p53 stress- and DNA-damage responses in neuroblastoma and breast-cancer. Firstly, I will present a generally applicable method for integrating tumour data into patient-specific dynamic models of cancer signalling. Secondly, I will show how patient-specific modelling of the JNK-p53 response network can stratify neuroblastoma patients. Thirdly, I will present our progress on modelling the cell-to-cell variability during the development of drug resistance. Both our theoretical and experimental results indicate that so-called cell-ensemble modelling can be used model the selective pressure of chemotherapy on cancer-cell populations.

[1] Fey, D. et al. (2015) "Signaling pathway models as biomarkers: Patient-specific simulations of JNK activity predict the survival of neuroblastoma patients" Science Signalling 8(408): ra130. [2] Kim, J., B. Schoeberl (2015). "Beyond static biomarkers - The dynamic response potential of signaling networks as an alternate biomarker?" Science Signaling 8(408): fs21. [3] Fey D, Kuehn A, Kholodenko BN (2016) "On the personalised modelling of cancer signalling" IFAC-PapersOnLine 49(26):312-317

10:50 [Bo Zhou](#), [Yiwu Yan](#), [Kikuye Koyano](#), [Yi Zhang](#), [Xinshu Xiao](#), [Michael Freeman](#) and [Wei Yang](#)

Comprehensive Proteogenomic Characterization of Human Prostate Cancer Cells Reveals Many Missing Proteins and Novel Protein Variants

SPEAKER: [Wei Yang](#)

ABSTRACT. Prostate cancer is a leading male cancer in the world, especially in industrialized countries. Nevertheless, proteome-wide analysis of human prostate cancer cells remains scarce, hindering our understanding of prostate cancer development and

progression at the systems level. Here, we report the most comprehensive proteogenomic profiling study of human prostate cancer cells undertaken to date. A total of 11,759 protein groups, corresponding to 10,561 human genes, were identified with a false discovery rate of $\leq 1\%$. Of these, 51 “missing proteins” were identified with high-stringency mass spectrometry evidence. Absolute quantification of all protein groups suggested that the abundance of proteins identified as relevant to prostate cancer spans five orders of magnitude, and that the identified “missing proteins” are of very low abundance (median < 2,000 copies per cell). Owing to the relatively high (median = 45.0%) protein sequence coverage, protein isoforms encoded by 755 genes were distinguished. In addition, our deep proteogenomic analysis identified 291 proteogenomic peptides, including 227 novel peptides derived from 165 protein variants. Through targeted mass spectrometry quantification of proteogenomic peptides of interest in seven prostate cell lines, the N-terminal extension form of ZDHHC20 was found to be much more abundantly expressed in bone metastasis-derived PC3 cells than in other cell lines. The proteogenomics data are expected to be a valuable resource for proteogenomics and prostate cancer research.

11:10 [Mohit Kumar Jolly](#), [Jason George](#), [Dongya Jia](#),
[Satyendra Tripathi](#), [Samir Hanash](#) and [Herbert Levine](#)
Quantifying epithelial-mesenchymal plasticity in cancer and its association with patient survival
SPEAKER: [Mohit Kumar Jolly](#)

ABSTRACT. Epithelial-to-Mesenchymal Transition (EMT) and its reverse Mesenchymal-to-Epithelial Transition (MET) often play crucial roles in cancer metastasis and drug resistance. Recent reports highlight that EMT and MET are not ‘all-or-none’ processes, instead cells can attain a hybrid epithelial/mesenchymal (E/M) phenotype. But, a hybrid E/M phenotype has been tacitly assumed to be ‘metastable’ that can be attained only transiently en route to EMT/MET, and remains poorly characterized. Rapid progress in mapping the regulatory networks for EMT/MET has enabled developing computational systems biology models to characterize a hybrid E/M phenotype. Here, using mechanism-based mathematical modeling, we identify a set of ‘phenotypic stability factors’ (PSFs) – OVOL2 and GRHL2 – that can help maintain cells in a hybrid E/M state. Next, we identify H1975 cells as stably maintaining a hybrid E/M state over multiple passages, and validate the role of these PSFs experimentally. We show that the knockdown of these PSFs that act as a ‘brake’ on full EMT drives cells to a fully mesenchymal phenotype. Finally, we devise a statistical model built upon gene expression profiles that can quantitatively predict where a given sample

lies on a scale of 0 (fully epithelial) to 2 (fully mesenchymal). Intriguingly, GRHL2 and OVOL2 were identified among the top predictors that could resolve a hybrid E/M phenotype, through an unsupervised screening, thereby reinforcing their suggested roles as PSFs. This model can recapitulate the experimentally observed behavior for multiple scenarios such as EMT induction, and unravels the association of a hybrid E/M phenotype with poor clinical outcomes across multiple tumor types. Collectively, our integrated theoretical-experimental approach enables a quantitative understanding of the role of a hybrid E/M state in tumor progression, and reinforces the emerging notion that cells in a hybrid E/M state may be more aggressive than cells in a full EMT state.

11:30 [Kyla A.L. Collins](#), [Timothy J. Stuhlmiller](#), [Jon S. Zawistowski](#), [Michael P. East](#), [Trang T. Pham](#), [Claire R. Hall](#), [Daniel R. Goulet](#), [Samantha M. Bevill](#), [Steven P. Angus](#), [Sara H. Velarde](#), [Noah Sciaky](#), [Lee M. Graves](#), [Gary L. Johnson](#) and [Shawn M. Gomez](#)

Defining subtype taxonomies and functional architectures of the breast cancer kinome

SPEAKER: [Kyla A.L. Collins](#)

ABSTRACT. Understanding the basis of complex cellular diseases such as cancer requires a multifaceted picture of cellular function and dysfunction. Here, we describe recent work integrating proteomic, expression, interaction and drug perturbation data to provide a broader view of the architecture of the breast cancer kinome and its behavior in response to targeted perturbations. Specifically, multiplexed small molecule inhibitors covalently bound to Sepharose beads (MIBs) were used to capture functional kinases in luminal, HER2-enriched and triple negative, basal-like and claudin-low breast cancer cell lines and tumors. Kinase MIB-binding profiles at baseline without perturbation were significantly uncorrelated to transcript abundance for many kinases and proteomically distinguished the four breast cancer subtypes. Understudied kinases were highly represented in the MIB-binding taxonomies and shown to be integrated in kinase signaling subnetworks with characterized kinases. Furthermore, we were able to identify regions of the kinome that are poorly characterized and/or poorly targeted by existing inhibitor therapies. Computationally it was possible to define subtypes using profiles of less than 50 of the more than 300 kinases bound to MIBs that included understudied as well as metabolic and lipid kinases. MIB-binding profiles readily defined subtype-selective differential adaptive kinome reprogramming in response to targeted kinase inhibition. Comprehensive MIBs-based capture of kinases provides a unique

proteomics-based method for defining functional kinase dynamics and subnetworks in cells and tumors that integrates poorly characterized kinases of the understudied kinase that is not possible using genomic strategies. Together, this systems view of the kinase presents potential opportunities for disease classification, identification of potential drug targets and the broader design of rational combination therapies.

11:50 [Xubin Li](#) and [Anil Korkut](#)

Phosphoproteomics-Guided Discovery of Effective Combination Therapies in Cancer

SPEAKER: [Xubin Li](#)

ABSTRACT. Quantitative description and classification of aberrant pathway activities in tumors can inform design of effective cancer therapies as most targeted agents inhibit tumor cell proliferation by blocking oncogenic signaling. However, development of such therapies has been a challenge since multiple oncogenic pathways can be co-activated in a given tumor and the pathway activation patterns vary substantially even within similar tumor types. Therefore, tumor-specific combination therapies are required to block multiple aberrant pathways. Our strategy involves an algorithmic approach to classify actionable oncogenic pathway signatures in large tumor/cell line cohorts and experimental testing of combination therapies specific to each oncogenic signature. For this purpose, we developed an integrated bioinformatics pipeline and a high-throughput experimental validation platform. We analyzed the expression and phosphorylation level changes of > 200 proteins in > 7000 tumor samples available from the TCGA project and > 600 cell lines. The phosphoproteomic data was collected at MDACC using the reverse phase protein array technology. We employed an iterative machine-learning algorithm that couples feature selection with clustering to identify a combination of discriminant and actionable protein biomarkers shared within each tumor subcohort. We identified the actionable targets within each subcohort specific oncogenic signaling signature in collaboration with domain experts and through database searches. Our results uncovered potentially actionable combinations of protein targets shared among subcohorts of tumors and cell lines over a large number of lineages. We are testing our predictions with drug combinations in cell lines that share the target oncogenic signaling signature. The most promising combination therapy candidates will be tested in patient derived xenograft models. We expect our strategy will expedite the global efforts for precision therapy development as the experimentally validated drug combinations will be nominated for basket clinical trials at MDACC and elsewhere.

10:30-12:30 Session 10C: Parallel Session II c: Cellular Signaling Networks II

CHAIR: [Tim Elston](#)

LOCATION: Old Dominion Ballroom

10:30 [Karol Nienałkowski, Katarzyna Andryka, Karolina Zakrzewska, Tomasz Jetka and Michał Komorowski](#)

Quantitative methods for detecting origins of interferons signalling sensitivity

SPEAKER: [Karol Nienałkowski](#)

ABSTRACT. Interferons (IFNs) signalling is a key mechanism to coordinate antiviral, anti-proliferative and immunomodulatory effects (1). A substantial amount of molecular details is known regarding IFNs signalling pathways, even though understanding, how information about complex mixture of IFNs is processed and translated into distinct cellular responses remains elusive (5,6). A good illustration is a sensitising effect of IFN type-I. Although the presence of this phenomenon is well known, its impact on signalling fidelity and biochemical mechanism that lead to these changes has not been recognised so far. Our experimental studies on IFNs signalling on mouse embryonic fibroblasts have shown that prior exposure to IFN type-I modify cellular response to IFN type-II stimulation. Precisely, information-theoretic analysis indicate higher sensitivity of pre-stimulated cells to the presence of IFN type-II in the intercellular environment. However, due to the complexity of signalling networks identification of origins of this mechanism cannot be addressed with solely experimental methods (7). Here we propose integration of high-throughput experimental single-cell measurements with a stochastic modelling in order to provide better understanding of mediation between IFNs type-I and -II signalling. Our solution is based on analysing intrinsic and extrinsic sources of heterogenous cellular response using unscented transformation and Sequential Monte Carlo methods (8,9). We have shown that origins of increasing sensitivity of pre-stimulated cells are changes in the initial cellular concentration of signal transducer and activator of transcription (STAT) proteins. Deciphering the mechanism that lead to more sensitive cellular response informs further research on novel therapeutic and diagnostic strategies to utilise the clinical potential of IFNs (5). 1. R.J.Critchley-Thorne et al. (2009) Impaired interferon signaling is a common immune defect in human cancer, Proceedings of the National Academy of Sciences.National Acad Sciences, 106:9010–5. 2. D.S.Aaronson (2002) A Road Map for Those Who Don't Know JAK-STAT, Science, 296:1653–5. 3. I.M.Kerr et al. (1994) Jak-STAT pathways and transcriptional activation in response to IFNS and other extracellular, Science. American Association for

the Advancement of Science, 264:1415–21. 5. B.S.Parker et al. (2016) Antitumour actions of interferons: implications for cancer therapy, Nat Rev Cancer, 16(3):131-144.. 6. L.Zitvogel et al. (2015) Type I-interferons in anticancer immunity, Nature Rev Immunol, 7:405-414.. 7. B.N.Kholodenko (2006) Cell-signalling dynamics in time and space, Nat Rev Mol Cell Biol, 7:165–76. 8. T.Toni, B.Tidor (2013) Combined Model of Intrinsic and Extrinsic Variability for Computational Network Design with Application to Synthetic Biology, PLoS Comput Biol, 9:e1002960. 9. S.Filippi et al. (2016) Robustness of mek-erk dynamics and origins of cell-to-cell variability in mapk signaling, Cell reports, 15:2524-2535.

10:50 [Jeffrey Law](#), [Sophia Orbach](#), [Bronson Weston](#) and [T. M. Murali](#)

Network Toxicology: Connecting the Dots in Protein Interaction Networks

SPEAKER: [Jeffrey Law](#)

ABSTRACT. Humans are constantly exposed to complex mixtures of environmental chemicals. Several ongoing efforts seek to increase our knowledge of chemical effects. For example, the EPA/NIH-funded ToxCast and Tox21 initiatives monitor the effect of chemicals on selected proteins using high-throughput screening assays. Toxicogenomic databases store gene expression profiles after chemical exposure. However, each dataset probes a different dimension of cell's response. Moreover, these experiments ignore complex networks through which proteins interact and computational methods to integrate these data are underdeveloped. These major barriers limit their usefulness of these data.

We propose computing toxicant response networks to address these challenges. For a chemical, such a network is composed of regulatory, signaling and physical interactions connecting proteins perturbed as a result of exposure to that chemical. We describe algorithms that connect the responding proteins in ToxCast/Tox21 assays in the context of the underlying network of regulatory and physical interactions. For well-studied chemicals, our networks are enriched in biological processes that are known to be perturbed by the chemicals. Toxicant response networks promise to reveal important intermediate proteins that have not have been tested and physiological processes that have not been previously implicated in connection with the chemical.

11:10 [Xia Wang](#), [Sarah Jungeun Kwon](#) and [Guang Yao](#)

Circadian clock protein Cry regulates cellular quiescence depth

SPEAKER: [Xia Wang](#)

ABSTRACT. The proper transition of mammalian cells between quiescence and proliferation is critical to tissue homeostasis and differentiation. Its deregulation is commonly found in many human diseases. Cryptochrome (Cry) is a transcriptional factor that is responsible for generating the negative feedback loop to maintain the circadian clock; its deregulated expression has been found to affect many physiological processes. Here, we focused on the role of circadian clock protein Cry in regulating the depth of quiescent cells. Experimentally, we showed that the overexpression or stabilization of Cry resulted in upregulation of c-MYC in quiescent rat embryo fibroblasts; however, cells did not go to a 'shallower' quiescent state as expected but a 'deeper' state. That is, a higher instead of lower serum concentration was required to drive cells out of quiescence in cells with upregulated Cry and Myc activities. Through systematic modeling of an array of possible regulatory network topologies between Cry and the Rb-E2F bistable switch that controls the quiescence-to-proliferation transition, we found that the 'deeper' quiescent state in response to increased Cry activity may be explained by upregulation of CDK inhibitors which counteract the c-MYC effect on the activation threshold of the Rb-E2F bistable switch. We further confirmed this model prediction in follow-up experiments. Our findings suggest a mechanistic role for circadian clock protein Cry in modulating the depth of cellular quiescence, which may have implications in varying potentials of tissue repair and regeneration in different times of the day.

11:30 [Jean-Michel Arbona](#), [Arach Goldar](#), [Olivier Hyrien](#),
[Alain Arneodo](#) and [Benjamin Audit](#)
Modeling the spatio-temporal replication program
SPEAKER: [Jean-Michel Arbona](#)

ABSTRACT. In the last few years, several models of the spatio-temporal replication program in eukaryotic cells were proposed in the literature. In these models, the frequency of new replication origin firing per length of unreplicated DNA along the S-phase, $I(t)$, is a fundamental quantity characterizing the DNA replication program dynamics. The $I(t)$ curves have been shown to present a universal bell shape in eukaryotes (Goldar, 2009), increasing until it reaches a maximum after mid-S-phase, and then decreasing to reach zero at the end of S-phase. Analytical modeling in Xenopus (Gautier, 2009) explained the initial increase by the progressive import of a factor required for origin activation, and the final decrease by a sub-diffusive motion of this factor. A simulation-based model (Goldar, 2008) also concluded for the need of a constant import rate of initiation factors and explained the final decrease by a coupling between the frequency of initiation and the fork density. A

recent simulation-based model in human cell (Gindin, 2014) was able to reproduce the $I(t)$ bell shape assuming an increasing reactivity of the initiation factors. After a careful analysis of these different models that enlighten their advantages and limitations, we propose a model where (i) origin firing results from a second-order reaction between unreplicated origins and unbound initiation factors and (ii) initiation factors remain bound to the replication forks until replication termination. This simple model that we corroborated by 3D simulations, fully accounts for $I(t)$ universal bell shape. The initial increase results from the recycling of the initiation factors and the final decrease is obtained when the time between two initiations become shorter than the time to replicate the mean distance between two origins. This modeling provide some prediction of the maximum value of $I(t)$ as a function of the replication fork speed and the density of potential origins.

Goldar, Arach, Marie-Claude Marsolier-Kergoat, and Olivier Hyrien. "Universal Temporal Profile of Replication Origin Activation in Eukaryotes." PLOS ONE 4, no. 6 (June 12, 2009): e5899.
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Gauthier, Michel G., and John Bechhoefer. "Control of DNA Replication by Anomalous Reaction-Diffusion Kinetics." Physical Review Letters 102, no. 15 (April 16, 2009): 158104.
doi:10.1103/PhysRevLett.102.158104.

Gindin, Yevgeniy, Manuel S Valenzuela, Mirit I Aladjem, Paul S Meltzer, and Sven Bilke. "A Chromatin Structure-based Model Accurately Predicts DNA Replication Timing in Human Cells." Molecular Systems Biology 10, no. 3 (March 28, 2014).
doi:10.1002/msb.134859.

11:50 [Nikoleta Tsvetanova](#) and [Mark von Zastrow](#)
Functional diversification of signaling by GPCR localization
SPEAKER: [Nikoleta Tsvetanova](#)

ABSTRACT. G protein-coupled receptors (GPCRs) are critical cell signaling molecules that also comprise the largest class of therapeutic drug targets. GPCRs are well known to signal upon ligand binding via production of the second messenger molecule, cyclic AMP (cAMP), at the plasma membrane, but recent evidence has indicated that various GPCRs may also signal after ligand-induced internalization. We

investigated the functional consequences of compartmentalized GPCR signaling, using the beta2-adrenoceptor (β 2-AR) as a model system. Global profiling of β 2-AR activation identified a core set of transcriptional target genes, and revealed that endocytosis is required for the full repertoire of downstream cAMP-dependent transcriptional responses. We then developed and applied an orthogonal optogenetic approach to definitively establish that the location of cAMP production is indeed the critical variable controlling the transcriptional response to β 2-AR signaling. Further, we found that β 2-AR endocytosis may provide a signaling 'checkpoint' that enables cells to respond uniformly to chemically distinct ligands acting on the same receptor while limiting spurious responses from non-cognate ligands. We are currently investigating the molecular mechanisms underlying location bias of signaling through functional genome-wide CRISPR interference-based gene silencing. Altogether, our findings establish a novel principle for functional diversification of signaling, based on the location of second messenger production, which underlies cellular discrimination of chemically distinct ligands.

12:10 [Jingyu Zhang](#), [Xiao-Jun Tian](#), [Yi-Jiun Chen](#), [Weikang Wang](#), [Simon Watkins](#) and [Jianhua Xing](#)

Cells read TGF-beta temporal information through a nested relay mechanism

SPEAKER: [Jingyu Zhang](#)

ABSTRACT. Cells live in ever-changing environment and need to reliably receive, decode, and transmit information of extracellular signals such as their strength and duration, so cells can respond appropriately. It is still an open question how cells distribute and integrate information through an intertwined network, and generate either adaptive or sustained responses.

TGF-beta is a multifunctional cytokine that regulates many important cellular processes. For a long time people are puzzled by the paradoxical roles of TGF-beta, for example, it functions as both tumor suppressor and tumor growth/metastasis promotor. Through integrated modeling and quantitative measurements we uncovered a novel nested relay mechanism that allows cells to read the temporal information of TGF-beta, and generate Snail1 expressions with different temporal profiles. We expect the mechanism to be general for signal transduction. We also identified a modified positive feedback loop network motif that can achieve seeming opposite tasks of being robustly against noises and having fast response time. The motif again appears frequently in networks regulating processes such as cell differentiation and immune responses.

Given the importance of TGF-beta signaling and the amount of existing studies on it, the new discovery is rather surprising. We argue that this work is a good example why an integrated approach including modeling and quantitative experimental studies is needed to study complex cellular process. Some key features of the system, such as the temporal and spatial evolution of different phosphorylation forms GSK3, have escaped from observation in the past. The work also emphasizes the importance of “temporal dynamics” on understanding biological systems and on biomedical interventions.

12:30-14:00 Session : Tuesday Lunch

LOCATION: Commonwealth Ballroom

14:00-16:30 Session 11: Tuesday Afternoon

CHAIR: [Julia Lazar](#)

LOCATION: Colonial Hall

14:00 [Naama Barkai](#)

Keynote Talk: How budding yeast allocates its translation resources

SPEAKER: [Naama Barkai](#)

15:00 [Shannon Hughs](#)

NIH/NCI Talk

SPEAKER: [Shannon Hughs](#)

15:30 [Coffee Break](#)

Tuesday Afternoon Coffee Break

SPEAKER: [Coffee Break](#)

16:00 [Tim Elston](#)

Mathematical models for cell polarization and gradient sensing

SPEAKER: [Tim Elston](#)

ABSTRACT. Directed or “polarized” growth and the detection of chemical gradients are two fundamental cellular processes. Here we combine mathematical modeling and analysis with various experimental approaches to investigate the molecular mechanisms that underline both processes during the mating response of yeast. Our analysis reveals a novel method for gradient sensing and insight into the biochemical mechanisms that either ensure the establishment of a unique site for polarized growth or allow multiple sites to coexist.

16:30-18:30 Session 12A: Parallel Session III a: Cellular Signaling Networks III

CHAIR: [Tm Murali](#)

LOCATION: Brush Mountain A & B

16:30 [Cemal Erdem](#), [Alison M. Nagle](#), [D. Lansing Taylor](#),
[Adrian V. Lee](#) and [Timothy R. Lezon](#)

Insulin receptor substrate (IRS) dictates differential responses to insulin and insulin-like growth factor I (IGF1) stimulation

SPEAKER: [Cemal Erdem](#)

ABSTRACT. The downstream signaling through insulin receptor and insulin-like growth factor I (IGF1) receptor are different in normal and disease states. Under normal conditions, IGF1 is a proliferation agent whereas insulin is one of the regulators of glucose homeostasis. Multiple investigations have shown evidence of similar functions and associations of the two hormones in cancer progression, cell proliferation, and evasion of apoptosis. Here, new insights on the mechanisms of differential MAPK and Akt activation are revealed by an iterative systems biology approach. The mechanistic network modeling here provided a framework to elucidate experimental targets downstream of two receptors, which were treated as indistinguishable in previous models. The model included cascades of both mitogen-activated protein kinase (MAPK) and Akt signaling, as well as the crosstalk and feedback loops in between. The parameter perturbation scanning yielded new experimental hypotheses on how differential responses of MAPK and Akt originate. Complementary to our previous efforts, the results suggested that SOS activation through IRS is critical to inducing greater MAPK activation in IGF1 stimulated cells. Secondly, the negative feedback from Akt to IRS is predicted to play a key role in the enhancement of Akt activation, seen in IGF1 stimulated cells with E-Cadherin knock-down. Third, the feedback from ribosomal protein S6 kinase (p70S6K) on IRS is predicted to differentially affect Akt activation under IGF1 and insulin stimulated cells. The experimental validation of the last prediction showed that there indeed is a difference in the regulation of Akt activity in response to different stimuli. Our results, computational and experimental together, showed the importance of interactions of the adaptor protein IRS in activation/inhibition of these specific cascades in breast cancer cells.

16:50 [Elin Nyman](#), [Hao Li](#), [William Lövfors](#), [Thirza Poot](#),
[Niclas Bergqvist](#), [Peter Strålfors](#) and [Gunnar Cedersund](#)

An expandable, multi-level, and multi-scale model to simulate drug simulations for type 2 diabetes and its complications

SPEAKER: [Elin Nyman](#)

ABSTRACT. Type 2 diabetes and its complications are multi-level (intra-cellular to whole-body) and multi-scale (seconds to years) diseases, and to properly understand the action of potential drugs, these aspects need to be understood in combination. Such an understanding can only be obtained using systems

pharmacology approaches, combining large amounts of data with mathematical modelling. However, all data cannot be considered simultaneously, since the complete modelling problem is too big. We have therefore developed an iterative approach, where sub-systems first are examined in isolation, and then integrated into a growing understanding of the whole.

The main key for breaking down the whole-body level into organs, is that we have experimentally measured their input-output profile, using arterovenous difference data. These data allows us to consider each organ as an isolated sub-problem, to easily switch between different versions of organ models, and to have a way to combine *in vitro* cell experiments with the whole-body level.

Using this approach, and 15 years of iterations between experiments and modelling, we have on the cellular level understood the mechanistic origin of insulin resistance in adipocytes: a malfunctioning feedback between the proteins mTORC1 and IRS1. Using the organ-flux data, we have embedded this detailed model in a whole-body and patient-specific model, which is a modification of a model already accepted by the FDA as a possible replacement for test animals when certifying insulin pumps. Finally, for the multi-scale long-term translations, we have integrated our multi-level model with weight-gain and disease progression models.

The combined model is already at use in several drug development companies, and is currently being refined and tested in some of the world's biggest clinical studies: SCAPIS and UKBIOBANK.

17:10 [Ping Wang](#) and [Xiao-Peng Zhang](#)

The link between dynamic modes of p53 and cell-fate decision in the DNA damage response

SPEAKER: [Xiao-Peng Zhang](#)

ABSTRACT. As a well-known tumor suppressor, p53 plays a key role in cell fate decision in cellular response to various stresses. It has been reported that p53 dynamics are stimulus-dependent, and different modes of p53 dynamics lead to distinct cellular outcomes. In this work, we developed a network model of p53 to explore how p53 dynamics modulates cell fate in the DNA damage response. We found that p53 exhibits three modes of dynamics in response to DNA double-strand breaks (DSBs). Upon mild damage, p53 shows persistent pulses and induce cell cycle arrest. For severe damage, p53 exhibits two-phase dynamics: a series of pulses appears to induce cell cycle arrest in the early phase, and p53 levels switch to high constant levels to trigger apoptosis in the late phase. Moreover, the number of pulses in the first phase drops with increasing DNA

damage. When DNA damage is extremely severe, p53 directly rises to high levels and induces apoptosis quickly. We proposed that the alternation in the predominance of positive and negative feedback loops results in the transition of p53 dynamics from pulses to high constant levels. Our results suggested that different modes of p53 dynamics directs cells toward distinct cellular outcomes.

17:30 [Anand Banerjee](#), [John Tyson](#) and [Ajit Joglekar](#)
Mathematical modeling of an “ectopic” spindle assembly checkpoint
SPEAKER: [Anand Banerjee](#)

ABSTRACT. The Spindle Assembly Checkpoint (SAC) is a complex surveillance mechanism that ensures the fidelity of chromosome segregation during mitosis. To probe the mechanism by which SAC signal is modulated during mitosis, the Joglekar lab has engineered an ectopic, kinetochore-independent SAC activator, the “eSAC”, that stimulates the signaling cascade of the SAC, and arrests cells in mitosis. The time spent in mitosis by individual cells in the presence of eSAC activation shows nonlinear dependencies on the concentration of eSAC (dose-response curves).

By combining a previous SAC model (He et. al., PNAS, 108(24), 2011) with details of eSAC, we have developed a stochastic mathematical model which explains the complex dose-response characteristics of eSAC. By doing so, we have also arrived at a plausible mechanism of how the SAC signal is maintained as the number of unattached kinetochores decreases over time during mitosis. Briefly, in the presence of multiple unattached kinetochores, SAC proteins are sparsely distributed among KNL1 molecules on unattached kinetochores. This leads to a steady SAC signal generated by multiple, weakly signaling kinetochores. In contrast, when only a few kinetochores are unattached, multiple SAC proteins are recruited per KNL1. By a synergistic effect, a small number of unattached kinetochores produce a strong anaphase-inhibitory signal. Together, these mechanisms ensure a steady SAC signal for the full duration of mitosis.

17:50 [Sarah Kwon](#), [Xia Wang](#) and [Guang Yao](#)
Controlling Quiescence Heterogeneity by an Rb-E2F Network Switch
SPEAKER: [Guang Yao](#)

ABSTRACT. Quiescence is a “sleep-like” non-proliferative cellular state. Reactivating quiescent cells (e.g., fibroblasts, lymphocytes, and stem cells) to proliferate is fundamental to tissue repair and regeneration. Often described as the “G0 phase”,

quiescence is in fact not a homogeneous state. As cells remain quiescent for longer durations, they move progressively “deeper” into quiescence, exiting from which requires prolonged and stronger growth stimulation. Nevertheless, deep quiescent cells can still re-enter the cell cycle under physiological conditions, distinguishing them from senescent cells. Underlying mechanisms of quiescence heterogeneity remain an enigma, and represent a currently underappreciated layer of complexity in growth control. Previously, we have shown that the retinoblastoma (Rb)-E2F pathway functions as a bistable switch that controls the all-or-none transition from quiescence to proliferation. Here by coupling modeling and single-cell measurements, we show that quiescence depth is controlled by the serum threshold to activate the Rb-E2F switch, which is in turn modulated by different Rb-E2F pathway components with different efficacies. We also found that the Rb-E2F activation threshold can be modulated by other cellular pathways including Notch and circadian pathways as well as metabolic responses. Such pathways crosstalk with the Rb-E2F pathway and together they form a quiescence regulatory network that determines the final quiescence states. Further elucidating the control of quiescence heterogeneity should provide the basis for future therapeutic strategies against hypo- and hyperproliferative diseases by counteracting abnormal quiescence depths in diseased cells.

16:30-18:30 Session 12B: Parallel Session III b: Cancer Systems Biology II

CHAIR: [Shannon Hughes](#)

LOCATION: Room 342 in Squires

16:30 [Alice Yu](#), [Andrew Gentles](#), [Angela Hui](#), [Joe Shrager](#), [Maximillian Diehn](#) and [Sylvia Plevritis](#)

Extracting dysregulated subnetworks in the non-small cell lung carcinoma tumor microenvironment

SPEAKER: [Alice Yu](#)

ABSTRACT. Non-small cell lung carcinoma (NSCLC) is one of the leading causes of death for both men and women. Early stage NSCLC is often treated with surgical resection alone, yet a significant fraction of patients' progress with local-regional and distant metastatic disease. An active research area is to identify which patients are likely to progress based on gene expression signature of their initial tumor. To date, many different signatures have been proposed. These signatures are likely related through underlying molecular processes of the tumor microenvironment. A better understanding of the tumor microenvironment, achieved by dissecting tumor-stromal interactions, promises a more robust

interpretation and evaluation of genomic signatures of prediction and prognosis. Recent studies have demonstrated that stromal cells within the tumor collaborate to drive cancer progression. To elucidate the role of stromal cells, we want to pinpoint the highly active biological networks within each cell-type. Current approaches of the tumor microenvironment include simply finding differentially expressed genes. The gene lists returned often have high false positive rates and are hard to interpret. Instead, we developed a new algorithm to extract protein-protein interaction subnetworks using gene expression data. This algorithm was applied to both RNA-Seq data from individually sorted stromal and epithelial cells within the NSCLC tumor microenvironment and from the Cancer Genome Atlas (TCGA). The resulting subnetworks elucidated cell-type specific functions within the tumor microenvironment with the goal of providing new insights into tumor-stromal mechanisms associated with tumor progression. This will aid with the interpretation of prognostic signatures and identification of tumor-stromal interaction drug targets.

16:50 [Richard Ballweg](#), [Andrew Paek](#) and [Tongli Zhang](#)

A Simple Formula for Fractional Killing

SPEAKER: [Richard Ballweg](#)

ABSTRACT. When chemotherapeutics are applied to tumor cells with the same or similar genotypes, some tumor cells are killed while others survive. This so called fractional killing can contribute to drug resistance in some cancer types. Drugs such as cisplatin not only activate p53 to induce cell death, but they also promote the expression of apoptosis inhibitors such as cIAP that protects cells through an incoherent feedforward loop. Due to this regulation, some cells activate their p53 quickly and undergo apoptosis, and cells that activate p53 slowly, survive. The incoherent feedforward loop along with the essential role of p53 activation timing makes fractional killing a complex dynamical challenge, which is difficult to understand using intuition alone. To better understand this process, we have constructed a representative model by integrating the control of apoptosis with the relevant signaling pathways. The model was then trained to recapture the observed properties of fractional killing and analyzed with nonlinear dynamical tools. Our analysis suggested a simple formula for fractional killing, where cell fate is a function of the bifurcation geometry and cell the trajectory. This formula predicts that cell fate can be altered in three possible ways: alteration of bifurcation geometry, alteration of cell trajectories or both. These predicted categories are able to explain existing strategies known to combat fractional killing and allow us to design novel strategies. In conclusion, we propose that our simple

formula can be used as a powerful tool for understanding and designing novel strategies that can combat fractional killing.

17:10 [Andrej Bugrim](#)

Dynamic network entropy as predictor of drug response in cancer cells.

SPEAKER: [Andrej Bugrim](#)

ABSTRACT. Many studies in the systems biology of cancer treat cell signaling networks as “molecular circuits” and aim to identify key elements responsible for disease. Alternatively, one may consider normal and cancer cells as different dynamic states of the molecular network and to treat disease onset as a global “phase transition”. Following this premise, we focus on dynamic network entropy – a statistical measure related to stability and robustness of network states. We investigate whether it can be used to address the problem of drug response in cancer cells. We assume that cellular homeostasis corresponds to a dynamically stable state of the molecular network. In cells where this state is not very robust the networks are likely to respond to drug-induced perturbations by undergoing a significant irreversible transition, resulting in a “drug-sensitive” phenotype. To the contrary, robust networks will relax back to the original state, exhibiting drug resistance. The likelihood of such transition can be approximated by the so-called “network entropy rates” which characterize network’s ability to dissipate perturbations. To test this hypothesis, we calculated network entropy rates for a set of approximately 100 cancer cell lines using gene expression profiles and curated data on protein-protein interactions. We investigated relations between entropy rates and sensitivity to several cancer drugs and found that for multiple network modules they significantly correlate with IC₅₀ values of drug response. Among those we found pathways related to targets of the drugs used in the study, indicating that dynamic stability of these elements is one of the determinants of drug sensitivity. We also demonstrated that entropy rates can effectively discriminate between sensitive and resistant cell lines and therefore can be used as variables in building predictive models of drug response.

17:30 [Dianira Erudaitius](#), [Andrew Huang](#), [Jacqueline Mantooth](#), [Garry R. Buettner](#) and [Victor G. J. Rodgers](#)

Systematic Approach to Understanding Selective Cancer Susceptibility to Pharmacological Ascorbate Therapy

SPEAKER: [Dianira Erudaitius](#)

ABSTRACT. Intravenous delivery of pharmacological ascorbate has shown to be a promising adjuvant in

the treatment of patients with pancreatic ductal adenocarcinomas. Administered as a series of infusions, pharmacological ascorbate generates high fluxes of extracellular hydrogen peroxide (H_2O_2), which is toxic to some cancer cells while not affecting normal cells. In vitro studies also indicate that cancer cells have a wide range of susceptibility to pharmacological ascorbateⁱⁱ and subsequently to extracellular H_2O_2 . The resulting H_2O_2 flux into cancer cells is believed to accumulate differently within the intracellular space when compared to normal cells. We hypothesize that internal H_2O_2 concentration has a steady-state value that is significant for cell susceptibility and independent of cell type. Although this has been alluded to, this value has yet to be quantified. Quantification of resulting intracellular H_2O_2 concentrations during pharmacological ascorbate therapy is necessary for understanding the relevant transport and reactions associated with this cancer treatment. Here, we develop a lumped parameter model for intracellular H_2O_2 quantification for any given cell type using experimental procedures to obtain necessary cell-specific parameters. We show the variations in cell parameters (i.e. membrane permeability via peroxiporin expression, catalase rates, cell size etc.) for various cell types are significant enough to alter the internal H_2O_2 concentration during ascorbate therapy, thereby impacting cell susceptibility. Further we found that the intracellular H_2O_2 is highly sensitive to the membrane permeability of the plasma and peroxisome membranes. In addition, flow cytometry displays elevated peroxiporin expression on ascorbate-susceptible cells. These results imply that plasma membrane permeability to H_2O_2 via peroxiporins is an important factor in the surviving fraction outcomes for susceptible cell lines. This work suggests that relatively high H_2O_2 -permeability of the plasma membrane of cells, either via peroxiporins or other mechanisms, is a critical factor in the success of therapeutic ascorbate in cancer treatment.

17:50 [Amrisha Bhosle](#) and [Nagashuma Chandra](#)

Co-target identification from context specific kinetic models of folate metabolism in methotrexate resistant cancers

SPEAKER: [Amrisha Bhosle](#)

ABSTRACT. Use of methotrexate (MTX), a widely used anti-cancer drug is being limited by the emergence of resistance. MTX inhibits several enzymes in the folate pathway to different extents. Despite a large number of studies, a quantitative understanding of target pathway dynamics in resistant cancers is majorly lacking. In this work, we constructed context specific kinetic models by integrating gene expression data for folate pathway enzymes from untreated, sensitive and resistant

variants of 7 cancer cell lines. The kinetic model contained 11 enzymatic reactions, 1 non-enzymatic reaction and 6 folate metabolites. Differences in pathway activity were identified from steady state fluxes and metabolite concentrations obtained for the different models. Fluxes and metabolite concentrations varied among untreated cancers suggesting inherent differences in pathway activity in different tissue types. More interestingly, the response of sensitive and resistant variants of each cancer type was also seen to vary in simulations of MTX-inhibition. However, accumulation of dihydrofolate at steady state in all sensitive models and decrease towards normal levels for their resistant counterparts was commonly observed for most cancers. Further, metabolic control analysis was used to identify crucial flux controlling enzymes in the folate pathway which can be targeted in MTX-resistant cancers.

16:30-18:30 Session 12C: Parallel Session III c: Special Session Due to Schedule Limitation

CHAIR: Jing Chen

LOCATION: Old Dominion Ballroom

16:30 Anca Stefan, Michelle Wong, Gang Liu, John Hartman, Ronald Pisoni, Bruce Robinson and Victor Andreev

A Black Box Model of Patient Response to Hemodialysis

SPEAKER: Anca Stefan

ABSTRACT. Observational studies have revealed a complex relationship between fluid overload, ultrafiltration rate (UFR) profile, systolic blood pressure (SBP), and mortality in end-stage renal disease (ESRD) patients. We present a black box model describing the relationship between the UFR profile during a hemodialysis (HD) session and SBP. We developed the model based on 5-year treatment data for approximately 10,000 hemodialyzed patients, provided by Visonex, LLC (Green Bay, WI). The data included patient demographics, outcomes (surviving, deceased, received transplant), and in-session SBP and rate of fluid removal (ultrafiltration rate, UFR) measurements. We modeled the effect of UFR changes on the patient's SBP by estimating a single input single output (SISO) black box non-linear model (Systems Identification Toolbox, MATLAB). Changes in the extracellular fluid volume, obtained by integrating UFR over time, represented the input signal, whereas the SBP fluctuations about the mean represented the output signal. This model can inform how modifying the UFR profile may favorably influence intradialytic SBP fluctuations, now tested as follows. After determining model parameters using measured data, various UFR profiles were simulated and fed into the model until a desirable output was

obtained, under the constraint that the same volume of fluid was removed. The process yielded a new UFR profile that allowed for lower amplitude fluctuations of SBP, thereby reducing circulatory stress. This method has potential therapeutic applications in that it can be used to minimize acute and chronic cardiovascular complications of fluid overload by determining an optimal UFR profile based on the patient's treatment history, including factors predicting switching from one type of intra-session SBP response to another.

16:50 [Wei-Feng Xue](#)

Nano-scale imaging and systems modelling of amyloid protein self-assembly

SPEAKER: [Wei-Feng Xue](#)

ABSTRACT. A number of devastating human disorders, for example Alzheimer's disease (AD), Huntington's diseases, type 2 diabetes and transmissible spongiform encephalopathies (TSEs), are associated with the abnormal folding and assembly of proteins. The net result of this misfolding is the formation of large insoluble protein deposits and small toxic and transmissible protein particles in a state called amyloid. What are the molecular mechanisms that govern the amyloid fibrils' potential to seed the formation of new aggregates, to propagate the amyloid state as prion particles, and to damage cells in amyloid-associated diseases? Here, a generic systems model describing the lifecycle of amyloid is presented in the context of experimental data derived from time dependent fluorescence kinetic assays and atomic force microscopy analysis of amyloid fibrils. We have developed AFM imaging approaches that are capable of resolving the fibril particle concentrations, their length distributions, as well as their toxic and infective potential to cells. With these approaches, we have shown that the disease-associated properties of amyloid can be linked to small nano-sized amyloid particles created through the breakage of amyloid fibrils. The approaches we have developed offer new opportunities to determine, quantify, and predict the course and the consequences in amyloid assembly of cytotoxic, infectious as well as functional amyloid systems.

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Xue and Radford, An imaging and systems modeling approach to fibril breakage enables prediction of amyloid behavior. Biophys J 105 (2013) 2811-2819.
Xue, Homans, Radford, Systematic analysis of nucleation-dependent polymerization reveals new insights into the mechanism of amyloid self-assembly. Proc Natl Acad Sci U S A 105 (2008) 8926-8931

17:10 [Karsten Kuritz](#), [Daniela Stöhr](#), [Nadine Pollak](#) and [Frank Allgower](#)

Reconstructing dynamic processes from high dimensional snap-shot data

SPEAKER: [Karsten Kuritz](#)

ABSTRACT. Motivation: Processes dynamics in heterogeneous cell populations are encoded in high dimensional single cell snap-shot data.

Reconstruction of the embedded low dimensional process manifold is successfully achieved by algorithms like wanderlust or diffusion maps.

However, the derived process scales e.g. wanderlust axis or pseudotime are in general not equal to the true scale on which the observed process evolves.

Results: We describe a universal and at the same time simple transformation scheme to recover the true process scale from any pseudotime algorithm. The transformation is based on the knowledge of the expected distribution of cells on the process scale which may be temporal, spatial or something else. We applied this method successfully to reconstruct the dynamics of the cell cycle machinery. Furthermore, we demonstrate the power of the method by reconstructing the spatial composition of multicellular tumor spheroids from snapshot data of dissociated cells. By reconstructing spatial spheroid composition from single cell data, we provide insights to the evolution of cell heterogeneity within tumor microenvironments and the associated responsiveness to therapeutics. **Outlook:** The method may be applied to lineage dynamics in cell differentiation or more sophisticated spatial geometries e.g. intestinal epithelial tissue. By transforming different psoudotime scales to the true process scale, the method can be used to integrate different experiments into a unified scale.

17:30 [Kun Xiong](#), [Alex Lancaster](#), [Mark Siegal](#) and [Joanna Masel](#)

Overrepresentation of feed forward loops can be driven by simple signal recognition, without the need for noise filtering

SPEAKER: [Kun Xiong](#)

ABSTRACT. In transcriptional regulatory networks (TRNs), a coherent type 1 feed forward loop (C1-FFL) is a structure in which one transcription factor induces the expression of another, and the two induce the expression of a target gene. An AND-gated C1-FFL can suppress responses to spurious and short-lived signals, and adaptation for this purpose is hypothesized to contribute to the abundance of C1-FFLs seen in real TRNs. In order to test this and similar adaptive hypotheses, we develop a null model that can computationally capture how the topology of TRNs is shaped by non-adaptive factors during evolution. Gene duplication and deletion shape TRN

topology very differently from the gain and loss of individual regulatory connections; our model captures the ratio between these mutation types in a realistic way. In addition, background stochastic “burstiness” in the expression of other genes might attenuate signals into forms quite different from the idealized transient signal previously considered in the C1-FFL context. We simulated the evolution of TRNs under i) selection for filtering out a brief square-wave spurious signal, ii) non-adaptive evolution to respond to an error-free signal in the presence of background stochasticity in gene expression, and iii) neutral evolution. We find that AND-gated C1-FFLs evolve readily under selection for a filter against the idealized spurious signal, but rarely under the other conditions. We also find that intrinsic noise in gene expression can promote the evolution of OR-gated C1-FFLs, suggesting that OR-gated C1-FFLs adapted for intrinsic noise might also explain the observed overrepresentation of C1-FFLs in real TRNs.

17:50 [Kjersti Rise](#), [Finn Drabløs](#) and [Morten Beck Rye](#)
**Aggregating RNA-Seq reads from multiple genes
in KEGG metabolic pathways improves
interpretability in gene expression pathway
analysis**

SPEAKER: [Kjersti Rise](#)

ABSTRACT. A common way to analyze gene expression data is by using pathway networks from databases such as KEGG, along with network visualization and analysis tools like Cytoscape. Applying gene expression data onto a KEGG network highlights changes in how the pathway is regulated, and can help understanding the biology. A major challenge with KEGG networks is that multiple genes are often found to be responsible for the same enzymatic reaction, and Cytoscape only shows the first listed gene in a given position, which can lead to incorrect interpretations. By manipulating the network files, it is possible to show all possible genes for a given reaction as a common box, and display fold change and p-values for each of these genes. However, displaying all possible genes gives a more complicated and messy analysis, which can be hard to interpret. We suggest a solution to simplify both analysis and interpretation, by using the counts from RNA-seq to collapse all genes in a KEGG box into one measurement. We show that the number of counts for genes can be used as a proxy for relative expression level between genes. Assuming that activity for an enzymatic reaction mainly depends upon the gene with the highest number of reads, and by weighting the reads on gene length and gene ratio, a new expression value is calculated for the KEGG box as a whole. The weighted counts for each box are then used for differential expression analysis, and these new up-/down-regulations can be applied to the

networks. Using prostate cancer as a model, we integrate RNA-seq data from two prostate cancer patient cohorts with data and prostate cancer metabolism data from literature. We show how using the reduced boxes instead of original genes gives more reliable pathways that are easier to interpret biologically.

18:10 [Nello Blaser](#), [Shirin Fallahi](#) and [Håvard G. Frøysa](#)

Model reduction under parameter uncertainty

SPEAKER: [Nello Blaser](#)

ABSTRACT. Introduction: The dynamics of biochemical networks can be modeled by systems of ordinary differential equations. However, these networks are typically large and contain many parameters. A model reduction procedure is presented in [1] where metabolites are reduced one at the time minimizing the difference between the original and reduced model. We extended this model reduction procedure using a new way to compare and select models.

Methods: Instead of considering reductions of only one metabolite at the time, we consider reductions of several metabolites simultaneously for different parameter sets sampled from a distribution. We clustered the dynamics of metabolites using a symmetric dissimilarity measure together with single linkage clustering. For the model consisting of four metabolites shown in the left panel of the figure, we show the full reduction procedure.

Results: We found that the best model reduction depended on the parameter and initial values of the full model. For some values, the iterative method in [1] did not find the best reduced model. For example, in the middle panel of the figure removing two metabolites is better than only removing one. We found that for sampled parameter values, the models with both intermediate metabolites removed form a cluster together with the original models as seen in the right panel of the figure.

Discussion: Our analysis shows that considering all possible model reductions simultaneously can lead to better reduced models since the model reduction algorithm in [1] can be sensitive to parameter and initial values. Cluster analysis enables us to include parameter uncertainty in the model reduction, where the clusters consist of models with similar dynamics.

Acknowledgements: This research was supported by the Research Council of Norway through grant 248840.

References: [1] Shodhan Rao, Arjan van der Schaft, Karen van Eunen, Barbara M. Bakker, and Bayu

Jayawardhana. A model reduction method for biochemical reaction networks. BMC Systems Biology, 8(1):52, 2014. URL <http://dx.doi.org/10.1186/1752-0509-8-52>.

18:30-20:30 Session 13: Poster Session I

We ask all posters be displayed in both poster sessions. For poster presentation, please check the poster presentation assignment page for detailed poster numbers.

LOCATION: Commonwealth Ballroom

18:30 [Jae-Seung Yeom](#), [Tanya Kostova-Vassilevska](#), [Peter Barnes](#), [David Jefferson](#) and [Tomas Oppelstrup](#)

Simulating the Evolutionary Dynamics of Single-stranded RNA Virus Populations

SPEAKER: [Jae-Seung Yeom](#)

ABSTRACT. Infection, replication and mutation are the key mechanisms governing the population dynamics of viruses and driving their evolution. In particular, RNA viruses have the high mutation rates which enable them to form highly diverse populations within a single host, evade immune responses and develop resistances to drugs. The advent of next generation sequencing platforms opens up the possibility of understanding virus evolution at the molecular level. However, virus evolution is a multi-scale process, involving multiple entities, e.g. heterogeneous host cells and receptors, and intracellular and extracellular mechanisms. Understanding this complexity necessitates the development of a multi-scale model that is computationally challenging and thus requires high-performance computing. We present an exploratory simulation model to study the evolution of heterogeneous virus populations in heterogeneous cell environments. This is a unique model that operates at three scales capturing the core of the evolutionary process. To the best of our knowledge, this is the first HPC-based simulation of its kind. Our model algorithmically represents key known or hypothesized biological mechanisms in a computationally feasible way. This can help biologists to test what-if scenarios and gain insights into the evolutionary dynamics of RNA viruses in a cell culture with less effort and resources in a shorter amount of time. The model does not aim to substitute for lab experiments, but to guide them and to speed up knowledge discovery. We simultaneously simulate the extracellular and the intracellular activities of RNA viruses, explicitly represented as nucleotide (NT) and amino acid (AA) sequences, as well as the diffusion of virus particles among cells. The simulation produces the quasispecies population evolved from initial viral and cell populations as a result of genotype-specific replication. Given NT/AA frequencies available in public databases, our model tentatively scores each

genotype's replication capabilities. This is a novel data-driven method, designed to explore hypotheses.

18:30 [Daniel Sevin](#) and [Uwe Sauer](#)

Nontargeted *in vitro* metabolomics identifies wide-spread enzyme promiscuity in *Escherichia coli*

SPEAKER: [Daniel Sevin](#)

ABSTRACT. Catalyzing biochemical reactions with high specificity has traditionally been considered a hallmark of metabolic enzymes, which are thought to have evolved from catalytically inefficient and unspecific ancestors. Accumulating evidence, however, suggests that many extant enzymes have retained their ability to act on multiple substrates or catalyze different reactions at physiologically relevant rates. Here, we report our results of testing all known metabolic enzymes in *Escherichia coli* for catalytic activity towards hundreds of potential substrates by incubating them in a mixture of complex metabolome extracts. Our data reveal that enzyme promiscuity extends far beyond what is currently appreciated, and suggest that promiscuous enzymes played a key role for organisms to acquire new metabolic capabilities when confronted with adaptation to changing environments. We expressed and purified 1,043 known metabolic enzymes from *E. coli* using the ASKA collection. Each enzyme was separately incubated in a complex metabolome cocktail consisting of combined cellular extracts of *Escherichia coli* grown in different nutrient combinations supplemented with general enzyme cofactors. Over the time course of 15 minutes, aliquots of each reaction mixture were sampled and quenched. A total of 13,000 samples were analyzed using nontargeted flowinjection time-of-flight mass spectrometry, revealing temporal dynamics of 10,000 detected ions annotated as up to 1,500 metabolites based on accurate mass. Discovered promiscuous reactions were integrated into a genome-scale metabolic model of *E. coli* to investigate their contribution to the adaptability of metabolism to changing nutrient availability in the environment. For 60% of the analyzed enzymes we detected ions depleting or accumulating over time, corresponding to substrates and products of catalyzed biochemical reactions. Among these active enzymes, 70% affected at least one ion that did not correspond to any of their previously known reactants, suggesting promiscuous activity. By comparing the molecular structures of annotated novel reactants with known reactants, we noted that for some enzymes the structures were highly similar, consistent with the concept of "substrate promiscuity" according to which enzymes can catalyze the same biochemical reaction with closely related substrates. In other cases, novel and previously known reactants were structurally

dissimilar, suggesting that these enzymes were able to catalyze mechanistically different reactions (also referred to as “reaction promiscuity”). The newly discovered promiscuous activities of several enzymes were (and are being) validated using enzyme assays and deletion mutants. Analyzing potential roles of this wide-spread promiscuity on metabolism within a genome-scale metabolic model suggest that promiscuous enzymes expand the metabolic capabilities in adapting to novel environments (i.e. accessing novel nutrient sources). We will further discuss the implications of wide-spread enzyme promiscuity for biotechnology and medical research. We present the first global enzyme activity screen, revealing unprecedented insights into the unexpectedly diverse catalytic capabilities of metabolic enzymes.

18:30 [Sen Liu](#)

A Dynamic KaiA-KaiC Interaction Maintains the Oscillation of the KaiABC Circadian Clock

SPEAKER: [Sen Liu](#)

ABSTRACT. The design of biological oscillators is an intriguing topic in Synthetic Biology. Although there have been many artificially designed biological oscillators, none of them has a period of around 24 hours like a circadian clock oscillator, especially solely based on proteins. The core circadian oscillator of cyanobacteria consists of three proteins, KaiA, KaiB, and KaiC. This circadian oscillator could be functionally reconstituted in vitro with these three proteins, and therefore has been a very important model in circadian rhythm research. KaiA can bind to KaiC and then stimulate its phosphorylation, whereas KaiB antagonizes KaiA’s function leading to the de-phosphorylation of KaiC. Using this protein-based circadian clock oscillator as a model, we aim to find its controlling point and re-design this oscillator. To this end, we combined the tools in bioinformatics, evolutionary biology, protein design, molecular biology, and mathematical modeling to study the interaction between KaiA and KaiC. We found that there exist complicated but critical structural movements during the binding of KaiA and KaiC, and these movements are determinant to the oscillation of the KaiABC system. We further revealed that the KaiA has an asymmetric structural flexibility, which regulates its auto-inhibition and the interaction with KaiC. Based on our findings, it could be possible to redesign this oscillator with more interesting functionalities, which would provide useful insights to the design of protein-based oscillators.

18:30 [Bo Huang](#), [Ruizhen Yang](#), [Yanting Zhu](#), [Yang Li](#), [Feng Liu](#) and [Jue Shi](#)

Coupled feed-forward and feedback of

ATM/p53/Mdm2/Wip1 control cell type-dependent bimodal p53 dynamics and cell fate response
SPEAKER: [Bo Huang](#)

ABSTRACT. The importance of p53 dynamics is evident in its control over differential cellular responses to various stress stimuli. It was previously identified that a bimodal regulation of p53 dynamics modulated by DNA damage strength is crucial for cell fate control. Further single cell analysis revealed significant cell-type variation in this bimodal switch that correlated with the dose-dependent DNA damage response. While mammalian cell lines activated similar periodic pulsing of p53 followed by cell-cycle arrest at low DNA damage, they switched to distinct dynamics at high damage, i.e. monotonic increase or a single pulse of p53. Cell lines with monotonically increasing p53 underwent faster and more extensive damage-induced apoptosis than cell lines exhibiting a single p53 pulse. By combining single cell imaging with computational modeling, we uncovered a regulatory module of coupled feed-forward and feedback, involving ATM, p53, Mdm2 and Wip1, which differentially activates bimodal p53 dynamics, with expression of ATM key to determine the collective control strength. We also identified an effective strategy for re-sensitizing the apoptotic response in the cell lines resistant to DNA damage signaling by combinatorial inhibition of Mdm2 and Wip1. Our work results not only elucidate a cell-type dependent dynamic control of p53, but also point to p53 pulsing as a suppressive mechanism that renders resistance to DNA damage signaling.

18:30 [Geysson Javier Fernandez Garcia, Jayson Gutierrez, Diane Lafaundex, Supriya Sen, Yu Hsin Chen, Zhang Cheng and Alexander Hoffmann](#)

Integrated regulation of mRNA synthesis and decay decodes TNF signaling during inflammatory muscle-atrophy.

SPEAKER: [Geysson Javier Fernandez Garcia](#)

ABSTRACT. Pro-inflammatory cytokines such as Tumor Necrosis Factor alpha (TNF) have been implicated in the pathogenesis of skeletal muscle atrophy, a phenomenon commonly associated with many chronic systemic inflammatory diseases such as cancer and AIDS. Although the regulation of mRNA levels in response to TNF signaling has been studied extensively in the context of immune activation, such as in macrophages, the mechanisms that control the gene repression program, which is of relevance in muscle cells, are still poorly understood. Here, we examine quantitatively the genome-wide gene expression effects of TNF exposure, both in the short and long term. We characterize the regulatory strategies of dynamic gene induction and repression programs in skeletal muscle cells by measuring both

mRNA synthesis and decay rates, and connecting these via mathematical modeling. Our data points to a dominant role of synthesis control in the regulation of both gene induction and repression in response to TNF, but that mRNA half-life control determines the majority of temporal profiles of gene expression. Furthermore, our analysis unveils an unexpected gene expression strategies. We found a cluster of extracellular matrix genes whose sustained TNF-triggered downregulation is actually preceded by transient production overshoot. This suggests that beneficial and detrimental effects of TNF are linked but distinguished by a signaling dynamics. Our fine-grained data highlights the importance of signaling dynamics in mediating TNF effect on muscle cells, and critical interplay between synthesis and degradation control in shaping dynamic gene expression programs.

18:30 [Xiaochu Li](#), [Florice Gonzalez](#), [Birgit Scharf](#) and [Jing Chen](#)

Spatiotemporal model for pattern formation in phage-bacteria system

SPEAKER: [Xiaochu Li](#)

ABSTRACT. Phages and their host bacteria form ecosystems, which typically involve intriguing spatiotemporal dynamics. Previous studies on spatiotemporal dynamics of phage-bacteria systems mostly focused on growth of circular phage plaques on the bacterial lawn. Recent experiments demonstrated intriguing asymmetrical patterns when phages were inoculated at the edge of an expanding bacterial colony on the agar medium that allows bacterial motility. The bacteria-clear zone grows into sectorial shapes which could persist straightly, flare out, or close up, depending on the infection efficiency. We developed a model to address the pattern dynamics of the phage-bacteria system. We found that the observed sectorial patterns critically depend on negative impacts of the bacterial density on (1) bacterial motility, and (2) phage reproduction. With appropriate parameters, these two relationships cause “freezing” of bacteria-phage plaque boundaries as the bacterial colony expands radially outward, and lead to the sectorial pattern. Our model reveals how spatial niche partitioning emerges in a host-pathogen system, in which the pathogens rely on host, not only to reproduce, but also to spread spatially.

18:30 [Katherine Bland](#), [Weihua Guo](#), [Jiayuan Sheng](#) and [Xueyang Feng](#)

Investigate metabolic reprogramming of *Saccharomyces cerevisiae* for xylose-based fatty alcohol production via ^{13}C metabolic flux Analysis

SPEAKER: [Katherine Bland](#)

ABSTRACT. Medium chain fatty alcohols (C8-C12) are commonly used in surfactants, detergents, biofuels, and cosmetics. Sustainable production of medium chain fatty alcohols using renewable feedstock such as xylose has been recently achieved by expressing a xylose utilization pathway and a peroxisome-targeted fatty acyl-CoA reductase in yeast *Saccharomyces cerevisiae*. It was found that much higher yield of fatty alcohol was achieved by using xylose as feedstock rather than glucose. However, the reprogramming of metabolic fluxes of *Saccharomyces cerevisiae* under xylose-based fatty alcohol production remains largely unknown. To this end, we applied a systems biology approach, namely ¹³C metabolic flux analysis, to rigorously quantify the differences of carbon fluxes in central metabolic pathways of *Saccharomyces cerevisiae* between glucose-based fatty alcohol production and xylose-based fatty alcohol production. We found that metabolic flux of the pentose phosphate pathway dramatically increased in xylose-based fatty alcohol production while metabolic flux towards the byproduct ethanol significantly decreased, which accounted for the improved yield of fatty alcohol under xylose fermentation. In addition, the cell maintenance energy was recognized as a rate-limiting step of xylose-based fatty alcohol production. Based on these discoveries, we next optimized the bioprocesses and successfully improved the titer of fatty alcohol to 0.6 g/L, which represents the highest production of medium chain fatty alcohols from xylose.

18:30 [Qi Song](#), [Ruth Grene](#), [Lenwood Heath](#) and [Song Li](#)
CoReg: Identification of co-regulators in genome scale transcription regulatory
SPEAKER: [Qi Song](#)

ABSTRACT. Transcription factors usually function as co-regulators to synergistically induce or inhibit expression of their target genes. In recent years, genome-scale gene regulatory networks have been generated for multiple organisms including both human and *Arabidopsis*. Existing module-finding algorithms fail to capture transcription co-regulators in these large-scale networks because these algorithms usually search for groups of densely connected genes (nodes) rather than co-regulating genes. In this study, we developed a new computational tool, CoReg, to identify transcription co-regulators in large-scale gene regulatory networks. CoReg groups genes based on similarities of shared targets between regulators in a network. We applied hierarchical clustering followed by dynamic tree cut to identify co-regulatory modules. We tested our approach in *Arabidopsis thaliana* (*A. thaliana*), *Escherichia coli* (*E. coli*) and *Homo sapiens*

(*H. sapiens*) gene regulatory networks. Using these network data sets, we explored the performance of different similarity indices and compared them to existing module-finding algorithms (Walk Trap, Edge Betweenness and Label Propagation). We conducted network-rewiring simulations and found that CoReg+jaccard similarity index performed better than other methods in identifying true co-regulators from rewired networks. Furthermore, we integrated a cell type-specific gene expression data set for Arabidopsis root and a large-scale transcription network of Arabidopsis generated by DAP-seq. We applied CoReg to this integrated data set to identify cell type-specific co-regulators. Our study provides a new tool for dissecting the architecture of gene regulatory networks.

18:30 [Johannes Borgqvist](#) and [Marija Cvijovic](#)

Large scale simulations of a damage accumulation model in *Saccharomyces cerevisiae* reveal the benefit of dynamic damage retention in unicellular ageing

SPEAKER: [Johannes Borgqvist](#)

ABSTRACT. A key feature of ageing, in both multi- and unicellular organisms, is the accumulation of damage such as malfunctioning proteins. This evolutionary well-conserved feature can be studied in the baker's yeast *Saccharomyces cerevisiae* where one of the main aspects of damage accumulation is the distribution of damage between the mother and daughter cells after cell division. This distribution is partially characterised by the fact that the mother cell retains damage, and thus prevents it from leaking over to the daughter, in order to generate a young and healthy offspring. In this work we aim to elucidate the advantage of dynamic damage retention on a population level by using large scale simulations of a dynamical model representing the whole pedigree. The model consists of ordinary differential equations (ODEs) describing the formation of intact and damaged proteins for each cell in the population coupled with two discrete events corresponding to cell division and death respectively. After division, a new cell represented with a specific set of ODEs is introduced and when cell death occurs the corresponding set of ODEs are removed from the model. The expanding system of ODEs is reinitialised by using the damage retention parameter and the various so-called ageing strategies constitute different means by which cells can alter their retention capacity. By using this novel large scale setup in combination with efficient numerical simulations, we investigate the most optimal ageing strategy in terms of replicative potential, and viable population size. Our results suggest that dynamically changing the retention throughout the lifetime of an individual cell is the preferred division and damage segregation

strategy giving cells a direct selective advantage.

18:30 [Nidhi Menon](#) and [Caroline N. Jones](#)

Heparin-based hydrogel as a biomimetic 3D matrix for solid-phase growth factor presentation and cultivation of breast cancer cells

SPEAKER: [Nidhi Menon](#)

ABSTRACT. Interactions of cancer cells with their microenvironment play a critical role in their survival, differentiation, and progression. The cell microenvironment composed of the extracellular matrix (ECM), tumor interstitium and surrounding cells influences cell phenotype through a concoction of physical, mechanical and biochemical factors.

Association of growth factors (GF) with the extracellular matrix (ECM) *in vivo* enhances the duration and potency of GF signaling. Contributions of the 3D solid-phase microenvironment are not reflected in conventional *in vitro* cell culture techniques. The present study sought to develop a 3D solid-phase microenvironment using heparin-based hydrogel with epidermal growth factor (EGF) for slow, controlled release of the GF and to compare the effects of soluble and solid-phase EGF on a model breast cancer cell line. To reflect the *in vivo* tumor characteristics, we developed a 3D microenvironment that promotes self-assembly of cells into spheroids, demonstrated using breast cancer cell line MDA-MB-231. RNA-seq analyses of the molecular signatures of breast cancer can be linked to the phenotype quantified in our hydrogel platform with systems biology and analysis of the changes in parameters that lead to phenotype changes in the cancer cells. We aim to optimize the 3D tumor microenvironment to culture biopsies and isolated CTCs in the clinic for further studies on underlying molecular mechanisms driving site-specific metastasis, and other diagnostic and prognostic markers and therapeutic screening. Computational modeling approaches using our experimental platform may be used to provide further insight into tumor dynamics influenced by the microenvironment.

18:30 [Brittany Boribong](#), [Mark Lenzi](#), [Sarah Kadelka](#), [Stanca Ciupă](#), [Liwu Li](#) and [Caroline Jones](#)

Measuring neutrophil migration patterns using microfluidic devices and ODE modeling of the mechanistic molecular pathways

SPEAKER: [Brittany Boribong](#)

ABSTRACT. During sepsis, the current leading cause of death in hospitals, neutrophils migrate and accumulate in healthy organs instead of migrating toward the bacterial infection. This dysregulation of neutrophil migratory phenotype as seen in loss of directionality and oscillatory migration has been

reported by us in human burn patients with sepsis. The goal of the proposed work is to investigate the heterogeneity in neutrophil migration phenotypes during sepsis. We have developed a microfluidic device to measure neutrophil chemotaxis in an opposing chemoattractant gradient to quantify decision-making. We use two chemoattractants: a pro-resolution and pro-inflammatory chemoattractant to model how a cell makes a decision toward a bacterial infection or an inflammatory signal. Our hypothesis is that low-level pro-inflammatory ‘programming or training’ signals, such as lipopolysaccharide, have a central role in determining the final neutrophil phenotype and in the development of sepsis. Despite tremendous advances in the understanding of signaling molecules and pathways within neutrophils, our understanding of the directional decision-making process is limited, and consequently, our abilities to modulate the activity of neutrophils restricted. Using an ODE-based dynamical framework, we model the interaction of the mutually inhibitory GRK2 and GRK5 proteins and its role in decision-making. Our model results show a bimodal switch between high and low levels of GRK2, indicating that GRK2 may play a role in neutrophil decision-making process. We show that unstimulated cells preferentially migrate toward a pro-resolution signal over a pro-inflammatory signal. However, when primed with a low-dose of a pro-inflammatory mediator, higher ratios of cells migrated toward the pro-inflammatory chemoattractant with a higher velocity. In the future, we will extract cells based on their migration decisions and measure receptor levels to determine the underlying molecular mechanism that drives neutrophil decision-making to validate our computational model. Using this experimental data, we will derive molecular parameters for our model.

18:30 [Sean Mack](#), [Daniel Yarmovsky](#) and [Daniel Dwyer](#)
Modeling the Metabolic Response to Antibiotic Stress in Bacterial Pathogens
SPEAKER: [Sean Mack](#)

ABSTRACT. The surge in antimicrobial resistance requires urgent development of innovative approaches to address the numerous bacterial pathogen threats outlined by the CDC and WHO. Notably, a growing body of evidence suggests that the presumed fitness disadvantages of resistant pathogens conferred by expression of resistance genes is not fully accurate. Compounding this issue, the metabolic responses of pathogens to antibiotic stress surprisingly remain poorly understood despite our great appreciation of specific drug-target interactions. Numerous omics-driven studies focused on treatment of diverse bacterial species with antibiotics have noted a clear shift in metabolism without deeper computational examination. Arising

from these data is the increasingly attractive hypothesis that modification of metabolism is a key component of cell death of susceptible bacteria after antibiotic treatment. Further exploration of the relationship between metabolism, antibiotic stress, and resistance is clearly needed.

To address these gaps in our fundamental understanding, we have compared the metabolic behaviors of wild type and resistant strains *Escherichia coli*. Specifically, we have performed RNAseq to measure mRNA abundance wild-type, ampicillin resistant, and kanamycin resistant *E. coli*. Transcriptomic data were integrated with the genome-scale metabolic model for *E. coli* to generate metabolic flux predictions for the stressed and unstressed states. To compare these unique phenotypes, we are developing a computational pipeline that combines the strategies of numerous algorithms, yielding robust and testable predictions for differential states. Our preliminary findings highlight that pathogenic bacteria may reductively constrain their metabolism upon antimicrobial challenge. To validate and improve these predictions, we have recently initialized ¹³C fluxomics experiments, which will refine our view of the central carbon metabolism behaviors of these pathogens.

18:30 [Minghan Chen](#), [John J. Tyson](#) and [Young Cao](#)
A Model of the Control Mechanism for the Genetic Circuit in Caulobacter Cell Cycle
SPEAKER: [Minghan Chen](#)

ABSTRACT. The asymmetric cell division cycle in *Caulobacter crescentus* is controlled by a cascade of cellular processes from DNA replication and segregation to cytokinesis and cell division to ensure the progression of cell growth and production. The timing of these cellular functions is regulated by the biochemical and genetic logic circuitry which initiate precise temporal activation of a host of proteins. Though a full map of how the cell directs and coordinates diverse mechanisms and cell cycle modules is still unclear, the genetic circuit alone predominately controls cell cycle regulation.

With recent discoveries and more information such as temporal dynamics for mRNAs and spatial distribution for proteins made available, we established an elaborate gene-protein regulatory network to achieve the oscillating cell-type gene expression coordination, centering on five master regulatory proteins: CcrM, DnaA, GcrA, CtrA and SciP, which directly controls approximately 60% of the cell genes. We explicitly characterized the control mechanisms for three key aspects of the genetic circuit: DNA replication, the function of DNA Methyltransferases CcrM, and the interactions between the five regulators themselves.

Particularly, we have introduced mRNA variables which play a role in the successive translation of the five regulatory proteins over the course of the cell cycle. The genetic circuit network is cast into a deterministic computational model to explore how it involves cell cycle progression and cell differentiation as an integrated system.

Simulated results successfully reproduce the genetic circuit with an oscillating pattern and fits well with experimental data of both the proteins' and the corresponding mRNAs' temporal behavior. We hope to incorporate the genetic model with other separate cellular modules to build the whole picture of Caulobacter Cell Cycle in the future. A similar methodology applied to other bacterial genera may be useful to fields such as biomedical sciences and natural resources.

18:30 [Agris Pentjušs](#) and [Egils Stalidzans](#)

Genome scale metabolic model of Arabidopsis thalina for isoprenoid production

SPEAKER: [Agris Pentjušs](#)

ABSTRACT. Capacity of plants of converting light to different valuable products makes them highly relevant to "green factories". To reduce burden of arable land usage for valuable product production there is need to increase significant plant productivity. In this study to we use Arabidopsis thaliana genome scale model in a synthetic biology based approach to increase production of z-abienol and isoprene depending on light intensity and diurnal cycle. Genome scale model is primarily derived from annotation aracyc 13.0 in the Aracyc database. We are using linear programming to demonstrate model capability to produce biomass components (amino acids, nucleotides, lipids, starch, cellulose). Model structure uses cytosol, mitochondria, plastid, vacuole and peroxisome compartments. Compartmented reactions are mostly used for interaction analysis of light and diurnal cycle involved reactions. Kinetic model of MEP as plant isoprenyl precursor pathway located in plastids will be used in combination with genome scale model to assess the feasibility of kinetic model steady states suggested by optimizations.

18:30 [Andreas Weidemann](#), [Ulrike Wittig](#), [Maja Rey](#), [Martin Golebiewski](#) and [Wolfgang Müller](#)

Kinetics data information retrieval from the literature as public service

SPEAKER: [Andreas Weidemann](#)

ABSTRACT. Quantitative modeling of complex biological systems requires a large number of parameters such as kinetic constants and experimental conditions. Most of the data is buried in

a constantly and quickly growing number of scientific publications, thus not being available for computation. It is practically impossible for researchers to keep up with this data flood without support of computers and databases.

Our group maintains a database for the storage of such information namely SABIO-RK, a resource for biochemical reactions and their kinetic properties (<http://sabiork.h-its.org/>).

SABIO-RK is part of the data management node NBI-SysBio within de.NBI (German Network of Bioinformatics Infrastructure, <http://www.denbi.de/>) program which is a newly-established BMBF-funded initiative having the mission to provide comprehensive first-class bioinformatics services to users in life sciences. In this context our group provides a couple of services including the manual extraction of kinetics data from the literature upon user requests. The information extracted comprises the origin of the data (publication), kinetic parameters, kinetic formula and kinetic type, reaction, organism, tissue, strain, compartment, enzyme classification and experimental conditions. Extracted data are provided in a structured way either accessible via our web interface, or as spreadsheets, or as SBML files for direct import into modelling and simulation tools.

Currently, this service is still free of charge and not restricted to German scientists. Any requests can be made using the corresponding form (<http://sabiork.h-its.org/contactFormSabio>) or by email (sabiork@h-its.org).

- 18:30 [Adrián César-Razquin, Enrico Girardi, Mi Yang, Justyna Konecka, Giuseppe Fiume, Marc Brehme, Julio Saez-Rodriguez and Giulio Superti-Furga](#)
In-silico prioritization of transporter-drug relationships from drug sensitivity screens
SPEAKER: [Adrián César-Razquin](#)

ABSTRACT. In spite of increasing evidence showing that cellular drug transport is mainly, if not exclusively, carrier-mediated rather than via passive diffusion [1], most chemical compounds still lack an associated transporter that explains their entry and distribution in cells and tissues. Currently known drug transporters correspond to two main protein families [2]: the ATP-Binding Cassette (ABC) transporter family, whose members are often involved in xenobiotic efflux and drug resistance, and the large and heterogeneous family of SoLute Carriers (SLCs), which includes various cases of drug uptake. We recently argued that SLCs are a highly neglected gene group [3], with most of its members still poorly characterized, and thus likely to include many yet-to-be-discovered cases of drug transport.

We therefore mined a publicly available pharmacogenomics dataset involving 1001 molecularly annotated cancer cell lines and their response to 256 anti-cancer compounds [4] in order to prioritize new SLC/ABC-drug associations. To this end, regularized linear regression models (Elastic Net) were generated to predict drug response based on SLC and ABC data (expression levels, Single Nucleotide Variants, Copy Number Variations), and their predictive performance assessed. The best predictive models included some known transporter-drug pairs, such as SLC35F2-YM155 [5] or several cases involving the multidrug resistance protein ABCB1, together with other associations not yet described. We are currently carrying out experimental validation of these by using CRISPR-Cas9-based single genetic knockouts in haploid cells (HAP1) and in a panel of cancer cell lines.

[1] Kell et al., Nat.Rev.Drug.Disc., 2011 [2] Giacomini, Nat.Rev.Drug.Disc., 2010 [3] César-Razquin, Snijder, et al., Cell, 2015 [4] Iorio et al., Cell, 2016 [5] Winter et al, Nat.Chem.Biol., 2014

18:30 [Subrata Dev](#)

Optimal methylation noise for best chemotactic performance of E. coli

SPEAKER: [Subrata Dev](#)

ABSTRACT. In response to a concentration gradient of chemo-attractant, {*sl* E. coli} bacterium modulates the rotational bias of flagellar motors that control its run-and-tumble motion, to migrate towards regions of high chemo-attractant concentration. Presence of stochastic noise in the biochemical pathway of the cell has important consequence on the switching mechanism of motor bias, which in turn affects the runs and tumbles of the cell in a significant way. We model the intra-cellular reaction network in terms of coupled time-evolution of three stochastic variables, kinase activity, methylation level and CheY-P protein level, and study the effect of methylation noise on the chemotactic performance of the cell. A good performance consists of reaching the favorable region quickly and localizing there in the long time limit. Our simulations show that the best performance is obtained at an optimal noise strength. While it is expected that chemotaxis will be weaker for very large noise, it is counter-intuitive that the performance worsens even when noise level falls below a certain value. We explain this striking result by detailed analysis of CheY-P protein level statistics for different noise strengths. We show that when the CheY-P level falls below a certain (noise- dependent) threshold, the cell tends to move down the concentration gradient of the nutrient, which impairs its chemotactic response. This threshold value decreases as noise is increased,

and this effect is responsible for noise-induced enhancement of chemotactic performance. In a harsh chemical environment, when the amount of nutrient depletes with time, the amount of nutrient intercepted by the cell trajectory, is an effective performance criterion. In this case also, depending on the nutrient lifetime, we find an optimum noise strength when the performance is at its best.

18:30 [Wei He](#), [Ayesha N. Shahajan-Haq](#), [Diane M. Demas](#),

[Robert Clarke](#) and [William T. Baumann](#)

Mathematical modeling of the unfolded protein response in different breast cancer cell lines

SPEAKER: [Wei He](#)

ABSTRACT. Estrogen receptor positive (ER+) breast cancer is the most common type of breast cancer today. The major treatment of ER+ cancer is endocrine therapy that targets the ER signaling or estrogen production, using selective estrogen-receptor response modulators to block the effect of estrogen, aromatase inhibitors to stop the production of estrogen, or estrogen-receptor down-regulators to reduce the number of ERs. Although these therapies can improve overall survival, breast cancers often develop resistance to endocrine therapies, and this resistance represents a significant impediment to successful treatment. The unfolded protein response (UPR) pathway, which is elevated in endocrine-resistant cells, plays a role in mediating endocrine resistance by influencing the balance between apoptosis and autophagy. To better understand the role of the UPR in the development of endocrine resistance, we built an ordinary differential equation model of the UPR for three cell lines: MCF7 (endocrine therapy sensitive, estrogen dependent), LCC1 (endocrine therapy responsive, estrogen independent) and LCC9 (endocrine therapy resistant, estrogen independent). The UPR of these three cell lines is induced by the strong reducing agent, dithiothreitol (DTT), which blocks disulfide-bond formation and leads to endoplasmic reticulum stress. DTT stress is modeled as an increased flow of unfolded proteins into the endoplasmic reticulum. The mathematical model is constructed from quantitative measurements of key UPR signaling molecules XBP1, GRP78/BiP, eIF2 α and phosphorylated eIF2 α . The models of the three cell lines have the same structure, and a minimal change of parameter values in the LCC1 model can adequately recapitulate the data from MCF7 and LCC9 cell lines. This result leads to the hypothesis that UPR signaling is the same for these three ER+ cell lines, and that the acquisition of resistance is due to changes in the balance of UPR signaling. The model also can contribute to identifying new drug targets for reversing endocrine resistance.

18:30 [Hunter Flick](#), [Jiayuan Sheng](#) and [Xueyang Feng](#)
Systematic Optimization of Protein Secretory Pathways in *Saccharomyces cerevisiae* to Increase Expression of Hepatitis B Small Antigen
SPEAKER: [Hunter Flick](#)

ABSTRACT. Hepatitis B is a major disease that chronically infects millions of people in the world, especially in developing countries. Currently, one of the effective vaccines to prevent Hepatitis B is the Hepatitis B Small Antigen (HBsAg), which is mainly produced by the recombinant yeast *Saccharomyces cerevisiae*. In order to bring down the price, which is still too high for people in developing countries to afford, it is important to understand key cellular processes that limit protein expression. In this study, we took advantage of yeast knockout collection and systematically screened 194 *S. cerevisiae* strains with single genes knocked out in four major steps of the protein secretory pathway, i.e., endoplasmic-reticulum (ER)-associated protein degradation, protein folding, unfolded protein response and translocation and exocytosis. The screening showed that the single deletion of YPT32, SBH1, and HSP42 led to the most significant increase of HBsAg expression over the wild type while the deletion of IRE1 led to a profound decrease of HBsAg expression. The synergistic effects of gene knockout and gene overexpression were next tested. We found that simultaneously deleting YPT32 and overexpressing IRE1 led to a 2.12-fold increase in HBsAg expression over the wild type strain. The results of this study revealed novel genetic targets of protein secretory pathways that could potentially improve the manufacturing of broad scope vaccines in a cost-effective way using recombinant *S. cerevisiae*.

18:30 [Verena Koerber](#), [Bernhard Radlwimmer](#), [Pankaj Barah](#), [Matthias Schlesner](#), [Katrin Lamszus](#), [Guido Reifenberger](#), [Michael Weller](#), [Peter Lichter](#) and [Thomas Höfer](#)

Clonal evolution in glioblastoma

SPEAKER: [Verena Koerber](#)

ABSTRACT. Glioblastomas are highly diffuse tumors with very poor prognosis. Their critical anatomical location restricts therapeutic options, reflected in tumor recurrence typically within months after primary resection. How glioblastomas evolve under treatment and which role tumor heterogeneity plays in this process is of major interest in the search for new therapeutic approaches. To reconstruct glioblastoma evolution from tumor samples, we analyzed 22 pairs of matched primary and relapse tumors with whole genome sequencing and investigated their degree of genomic heterogeneity. This was achieved by modeling the sequencing read count data as a

sampling result from a mixture of genetically distinct subclones which correspond to the tips of a phylogenetic tree. Our analysis, restricted to a finite set of candidate trees, suggests that glioblastomas are heterogeneous tumors with two to three dominating subclones per tumor sample. The subclonal distributions support a model of branched evolution in which a common stem of mutations is shared by the entire tumor before additional cycles of mutation and selection shape genetically distinct subpopulations. Our data further indicates that relapse tumors do not directly evolve from subclones identified in the primary sample, but from common ancestor populations which are not recovered in the primary sample. Our findings shed light on the clonal evolution of glioblastomas, both between tumor initiation and primary lesion, and between primary lesion and recurrence. A thorough analysis of the mutations assigned to the tumor stem is ongoing and will help us to distinguish early from late mutations and thus gain insight into the early development of glioblastoma.

18:30 [Akshay Malwade](#), [Angel Nguyen](#), [Peivand Sadat-Mousavi](#) and [Brian Ingalls](#)

Predictive modelling of a batch filter mating process

SPEAKER: [Akshay Malwade](#)

ABSTRACT. Quantitative characterizations of horizontal gene transfer mechanisms are needed for understanding and predicting the dynamics of gene distribution in natural and engineered systems. In this study, we developed a mathematical characterization of plasmid conjugation between two bacterial populations (filter mating).

We mated two E.coli strains. The donors harboured the self conjugative, GFP-coding plasmid PKJK10. The recipients expressed RFP from the plasmid PSB1C3. Time series assays were made by flow cytometry to quantify the distribution of the three subpopulations involved in the filter mating process (GFP+/RFP- donors, GFP-/RFP+ recipients, and GFP+/RFP+ transconjugants). Corresponding measures of optical density determined the temporal variation in the abundance of each population.

We used the data to fit ordinary differential equation models of the process, based on previously published model frameworks. Model comparison tools were applied to arrive at an optimal model formulation, and the accuracy of the best-fit parameter estimates was assessed via uncertainty analysis. We tested the model's predictive power by comparing model simulation to experimental results that demanded extrapolation from the training data. These comparisons provide evidence that the model can be

successfully used as a predictive tool for characterizing horizontal gene transfer mechanisms in natural or synthetic systems. This work recently appeared in *Frontiers in Microbiology*.

18:30 [Vincent Noël](#), [Marcelo S. Reis](#), [Matheus H.S. Dias](#), [Lulu Wu](#), [Amanda S. Guimarães](#), [Daniel F. Reverbel](#), [Junior Barrera](#) and [Hugo A. Armelin](#)

SigNetSim : A web platform for building and analyzing mathematical models of molecular signaling networks

SPEAKER: [Vincent Noël](#)

ABSTRACT. Molecular biology is experiencing a revolution, in one part thanks to new technologies to measure and perturb biological systems *in vitro*, and also due to the growing importance of mathematical modeling which enables us to understand biological mechanisms in a more profound way. However, one crucial point in this transforming field is the need to provide completely new tools, which should be computationally efficient, versatile, and compatible.

To this end, we developed SigNetSim, a web platform written in Python and using the Django framework. SigNetSim uses Bootstrap as a graphical front-end, which makes it usable on most devices. It is designed to be installed on computation servers, with all the work being executed server-side.

Users can create and edit biological models in the standard SBML format. Additionally, the platform supports the SBML comp package, which allows the user to write hierarchical models, where models contains other SBML models as sub-models. This allows reuse of models, and simplify the writing of large models. SigNetSim performs simulation both for time series and steady states, and plots the results using JavaScript interactive libraries. It is partially compatible with SED-ML format, which stores simulation settings and allows users to easily reproduce simulations from literature. Moreover, SigNetSim can use combine archive format, which stores both the SBML model and the SED-ML simulation file into one file. The platform includes a simple database to store experimental data, which can be used to simulate models according to a set of initial conditions, or to fit models using a parallelized simulated annealing algorithm. Users can perform various types of dynamical analysis, including bifurcation analysis. SigNetSim also supports model annotation, following the MIRIAM guidelines.

Finally, SigNetSim is available on GitHub under GPLv3 license. As a case study, we present a model for mitogenic pathways in mouse Y1 tumor cells.

18:30 [Sang-Min Park](#), [Chae Young Hwang](#), [Daewon Lee](#),

[Jeong-Ryeol Gong](#) and [Kwang-Hyun Cho](#)

Cell-type specific optimized therapy for colorectal cancer based on dynamical analysis of variant network models

SPEAKER: [Sang-Min Park](#)

ABSTRACT. Colorectal cancer is becoming a major threat these days whereas only a part of patients respond to targeted anti-cancer therapies. Such heterogeneous responses of colorectal cancer patients are primarily due to the complex molecular interactions of cancer cells that are differentially wired according to the mutational profiles. Analysis of such diverse cancer networks is therefore required to develop precision medicine. In this study, we have reconstructed a colorectal cancer signaling network including four frequently mutated canonical pathways: mitogen-activated protein kinase, DNA damage, Wnt, and transforming growth factor beta signalling pathways. Based on this, we have developed colorectal cancer cell-type specific network models by employing discrete logic-based Boolean network modeling. We revealed the distinct dynamical characteristics of various cell-types by investigating the attractor landscape of each network model. Finally, we have identified an optimal drug combination for each network model by evaluating the drug responses on the basis of efficacy, toxicity, and potency. Our study provides a new insight into the optimized therapy for colorectal cancer.

18:30 [Matthias Guenther](#), [Sumit Deswal](#), [Wolfgang Schamel](#) and [Thomas Höfer](#)

Specificity and sensitivity of antigen sensing by the T cell receptor is enhanced by the co-receptor CD8

SPEAKER: [Matthias Guenther](#)

ABSTRACT. T cells scan body cells for pathogen-derived peptides that are presented by major histocompatibility complex (pMHC) molecules. To discriminate between self and foreign peptides, cytotoxic T cells express the T cell receptor (TCR) and the co-receptor CD8, both binding to pMHC. Several models of this process have been proposed, however, lacking molecular detail. Here, we combine dose response measurements for soluble pMHC tetramers of graded affinity to the TCR in the absence or presence of CD8 with mathematical modeling. Data simulation selected one particular mechanistic model of the TCR-pMHC-CD8 interactions. This model shows that CD8 enhances binding of pMHC to T cells. However, at the same time CD8 reduces the capability of low affinity pMHC to stimulate TCRs by hindering pMHC from binding to the TCR. In sharp contrast, CD8 increases the capability of high affinity pMHC to stimulate TCRs by allowing few pMHC to simultaneously bind to TCR and CD8 thereby

recruiting the CD8-associated kinase Lck to those TCRs. T cell activation data confirm this prediction, leading us to describe a detailed molecular mechanism in which CD8 enhances both the specificity and sensitivity of affinity-based antigen discrimination by T cells.

18:30 [Christian Lieven](#), [Moritz Beber](#) and [Nikolaus Sonnenschein](#)

Memote - A testing suite for constraint-based metabolic models

SPEAKER: [Christian Lieven](#)

ABSTRACT. Constraint-based metabolic models have become fundamental and trusted tools in systems biology. Several layers of biological information are combined in a compact format in order to describe a metabolic model. A richly annotated model is required for its various areas of application and represents a veritable knowledge base about an organism's metabolism. However, coherently describing a complex interlinked system such as metabolism is a challenge in and of itself that is only aggravated by the current lack of cohesive, widely-accepted, testable, and modern standards.

Here, we introduce memote (Metabolic Model Tests (<https://github.com/biosustain/memote>)), a Python package designed to run a given model through a set of hard and soft tests and generate a report that reflects model integrity. Soft tests focus on aspects that do not influence the performance of the model, such as syntactic conventions whereas hard tests determine whether a model is fully functional.

While memote can be run locally as a stand-alone testing suite, it shows its full potential when combined with web-based version controlling (Github) and continuous integration tools (Travis CI). Every tracked edit of a model automatically triggers the memote test suite, and generates a corresponding report that facilitates factual debate of model changes.

Thus, memote not only allows researchers to more quickly iterate through the design-build-test cycle but also provides the scientific community with a measure of quality that is consistent across setups, as well as an opportunity to interact and collaborate by establishing workflows for publicly hosted and version controlled models.

18:30 [Willian Da Silveira](#), [Ludivine Renaud](#), [Jonathan Simpson](#), [Matthew Huff](#), [William B Glen](#), [E. Starr Hazard](#), [Dongjun Chung](#) and [Gary Hardiman](#)

miRNA expression shifts as an initiator event in carcinogenesis induced by Bisphenol A in human prostate cells

SPEAKER: [Willian Da Silveira](#)

ABSTRACT. Introduction: Bisphenol A (BPA) is a chemical used in the production of polycarbonate plastics and is notable for its endocrine-disrupting effects acting as a xenoestrogen. Its ubiquitous nature in the environment is highlighted by the fact that 92.6 % of adults excrete BPA. Recently estrogens have been implicated as potential agents in the development and progression of prostate cancer. miRNAs act as gatekeepers in transcription modules, increasing the robustness of transcription networks. Objectives: We hypothesize that BPA exposure negatively impacts transcriptional programs via alterations in miRNA expression, resulting in less robust biological circuits that are more prone to unstable outputs that can ultimately lead to prostate cancer. Materials and Methods: We extracted RNA from Human Prostate Epithelial Cells (ClonetechsTM), derived from a 23-year-old male, and cultured in the presence or absence of two BPA doses (5 and 25 nM) and ethinylestradiol EE2 (0.1 nM) for 24 hours. RNAseq was performed on an Illumina HiSeq2500. DE mRNAs and miRNAs were determined using Limma. Correlation and systems analyses of DE mRNA and miRNAs were performed using multiMir and iPathwayGuide. Results and Discussion: With both BPA exposure conditions, hsa-miR-335-3p, hsa-miR-543, hsa-miR-424-5p, hsa-miR-548h-5p, hsa-miR-493-5p were the top 5 miRNAs when ranked by the number of affected mRNA targets. EE2 exhibited similar results, with the exception of hsa-miR-493-5p, which is ranked 6th, and hsa-miR-548d-5p, which is ranked third and is only up-regulated with EE2. All miRNAs noted impact cell cycle at a systems level. hsa-miR-335-3p is the top ranked miRNA across all three conditions and is linked to obesity and ER- α inhibition, well-known effects of BPA exposure Conclusion: BPA exposure, even at low doses, disrupts miRNAs involved in cell cycle regulation. This disruption suggests a loss of robustness in this system, which can potentially facilitate carcinogenesis.

18:30 [Shirin Fallahi](#), [Rune Kleppe](#), [Anders Goksøyr](#),
[Guttorm Alendal](#) and [Hans J. Skaug](#)
**Mathematical modeling of regulatory interactions
in the fatty acid synthesis pathway**
SPEAKER: [Shirin Fallahi](#)

ABSTRACT. Introduction: Exposures of Atlantic cod (*Gadus morhua*) to environmental contaminants such as PCB153, increase the levels of enzymes involved in fatty acid synthesis in cod hepatocytes. Mathematical modeling using non-linear differential equations may help to identify how this affects the synthesis rate of fatty acids and triglyceride stores in cod hepatocytes. Such models can also describe the dynamics of fatty acid synthesis and the flux at

different boundary conditions. In this study, we have used mathematical modeling to investigate the impact of feed-forward and feed-back regulatory interactions in the pathway as well as possible time delay for the reaction catalyzed by the multi-enzyme complex fatty acid synthase (FAS).

Method: Using mass action and Hill type kinetics, we constructed a model involving non-linear controlled differential equations. A synthesis pathway from citrate to triglycerides is assumed, including also palmitoyl-CoA and the mitochondrial import for subsequent beta-oxidation. In this pathway, palmitoyl-CoA is a feedback inhibitor of acetyl-CoA carboxylase and citrate is an allosteric activator. A non-competitive inhibition with regard to acetyl-CoA is assumed. Insulin and glucagon triggers are assumed as control variables to consider the effects of external disturbances on the system. The pathway with regulatory interactions is shown by the diagram.

Preliminary result: By non-dimensionalizing equations the number of parameters was reduced, and the steady state solutions were found analytically. Constraining the concentrations to be non-negative gave us valid parameters region. The stability of the steady state solutions was studied by investigation of eigenvalues of the Jacobian matrix of system of equations looking for bifurcation points.

Further work: We are studying how different choices of the control variables can affect the trajectory of the system and the stability of the steady state solutions.

Acknowledgements: This research was supported by the Research Council of Norway through grant 248840.

18:30 [Nicholas Butzin](#) and [Will Mather](#)

Crosstalk between diverse synthetic protein degradation tags in Escherichia coli

SPEAKER: [Nicholas Butzin](#)

ABSTRACT. Recently, a synthetic circuit in E. coli demonstrated that two proteins engineered with LAA tags targeted to the native protease ClpXP are susceptible to crosstalk due to competition for degradation between proteins. To understand proteolytic crosstalk beyond the single protease regime, we investigated in E. coli a set of synthetic circuits designed to probe the dynamics of existing and novel degradation tags fused to fluorescent proteins. These circuits were tested using both microplate reader and single-cell assays. We first quantified the degradation rates of each tag in isolation. We then tested if there was crosstalk between two distinguishable fluorescent proteins engineered with identical or different degradation

tags. We demonstrated that proteolytic crosstalk was indeed not limited to the LAA degradation tag, but was also apparent between other diverse tags, supporting the complexity of the *E. coli* protein degradation system.

18:30 [Moritz Beber](#), [Svetlana Galkina](#), [Henning Redestig](#), [Nikolaus Sonnenschein](#), [Peter St. John](#) and [Christian Diener](#)

Fast, easy, interoperable and reusable – the cobrapy infrastructure for constraints-based analysis of metabolic flux

SPEAKER: [Moritz Beber](#)

ABSTRACT. Constraints-based reconstruction and analysis (COBRA) is widely used to interpret and predict the interplay between genotype and metabolic fluxes. The community-developed cobrapy Python package implements functionality to read, write, edit, and adjust COBRA models and to perform simulations using numerous popular algorithms. Since the first releases in 2012, the cobrapy project has gained considerable attention thanks to its broad feature-set with extensive documentation, and to being free/open source software without any non-free dependencies. The core classes of cobrapy form a basic infrastructure for constraints-based modeling that is easy to reuse in other packages, facilitating the development of new functionality as well as increasing potential interoperability between packages. In order to simplify the implementation of new algorithms, we have drawn on our experiences with the early versions of cobrapy, the development of the strain design package cameo, and the mathematical modeling package optlang, to enhance the cobrapy core classes. Interaction with the software that actually solves the mathematical problem in the COBRA model is now provided by optlang, which greatly facilitates the implementation of new COBRA algorithms and encourages the contribution of new algorithms from the research community. Several simulation algorithms have already been refactored for increased readability and performance. Here, we present the new functionality and outline the way forward for the role of cobrapy as a freely available infrastructure package for efficient constraints-based modeling of metabolic flux in python.

18:30 [Jeong-Ryeol Gong](#), [Dongkwan Shin](#), [Jonghoon Lee](#) and [Kwang-Hyun Cho](#)

Analysis of phenotypic network changes along with the sequential occurrence of driver mutations during colorectal tumorigenesis

SPEAKER: [Jeong-Ryeol Gong](#)

ABSTRACT. Cells undergo an evolutionary process

such that cooperative cancerous characteristics are acquired along with the accumulation of somatic mutations during tumorigenesis. There is still a lack of systems biological understanding as to how the cancerous phenotypic characteristics change and how they are synergistically connected in cancer evolution processes. In our previous study, using a genome-wide analysis of the somatic mutations in colorectal cancer patients on the basis of a large-scale molecular interaction network, we found that a giant cluster of mutation-influencing subnetworks undergoes a percolation transition during colorectal tumorigenesis and ultimately results in a giant percolated cluster (GPC) that includes a set of genes closely related to the cancer development. In this study, to further investigate the cooperation of cancerous phenotypic characteristics in tumorigenesis, we projected the genes obtained from GPC onto a phenotypic network composed of 50 hallmark gene sets from MSigDB, to be named a Hallmark Gene Set Network (HGSN). By clustering patient-specific HGSNs according to the occurrence of driver mutations (e.g., APC, KRAS, PIK3CA, SMAD4, and TP53), we found that the HGSN becomes dense as driver mutations are accumulated in a defined order. When we categorized the hallmark gene sets according to the Weinberg's cancer hallmarks, we further found that a more malignant cancer has a higher density of the subnetwork related to the metastasis category. Taken together, we conclude that cancerous phenotypic characteristics are connected with each other cooperatively during colorectal tumorigenesis and that HGSN enables us to infer optimal anti-cancer targets that can prevent such critical connections among the cancer-related hallmark gene sets.

18:30 [Mor Miodovnik](#), [Axel Künstner](#), [Ewan Langan](#), [Detlef Zilkens](#), [Regine Gläser](#), [Eli Sprecherq](#), [John Baines](#), [Enno Schmidt](#) and [Saleh Ibrahim](#)

A distinct cutaneous microbiota profile in autoimmune bullous disease patients

SPEAKER: [Mor Miodovnik](#)

ABSTRACT. Bullous Pemphigoid (BP) is the most common autoimmune blistering disease in Europe. As both the incidence of the disease and the relative proportion of the elderly population continue to rise, it represents a significant medical burden. Whereas some progress has been achieved in defining genetic risk factors for autoimmune blistering diseases, no environmental agent has been conclusively identified. Emerging evidence suggests that host immunity may influence the skin microbiota while the latter modulates cutaneous immunity. Nevertheless, the relationship between skin microbial communities and autoimmune bullous disease has yet to be studied in humans. Here, we aim to characterize and compare

the skin microbiome of BP patients and healthy, age-matched controls at numerous body sites. Similar to what has been shown in healthy controls, the composition of skin microbiota in BP patients appears to be very divergent and site-specific. Microbial phylum abundances differ between perilesional sites of BP patients and the same anatomic locations of control patients. A distinct cutaneous microbiota profile, which correlates with BP, further strengthens the significance of commensal-host interaction on our immune system. Moreover, these results raise the possibility that the cutaneous microbiome may contribute to the pathogenesis of BP, with important implications for the treatment of this disease.

18:30 [So-Yeong Jang](#), [Jonghoon Lee](#), [Yunseong Kim](#),
[Dongsan Kim](#) and [Kwang-Hyun Cho](#)

Predicting the perturbation effects in biological networks based on linear system approximation modeling

SPEAKER: [So-Yeong Jang](#)

ABSTRACT. Owing to the development of high-throughput measurement technologies and the advancement of systems biology for network inference methods, the network models for molecular regulatory interactions are rapidly increasing and becoming more available. However, network analysis methods are still limited and often require very accurate nonlinear dynamic models. In particular, to predict the effects of any perturbation in the network components such as nodes or links, we need a detailed nonlinear mathematical model based on kinetic parameter estimation with time-series measurements. Such time-series measurements for parameter estimation limits constructing a large-scale dynamic network model. Hence, there is a pressing need to develop a new network analysis method with which we can predict the perturbation effects based only on network topology. In this study, we present such a novel method with a linear system approximation. Intriguingly, we could predict the perturbation effects with an accuracy of more than 60% based on network topology and mutation profiles of various cell types. The proposed method can be used to predict differential drug responses depending on cell types and also to identify new promising drug targets.

18:30 [Younghyun Han](#), [Juntae Kim](#) and [Kwang-Hyun Cho](#)
Predicting anticancer drug responses using deep learning based on cancer cell line gene expression profiles and drug molecular fingerprints

SPEAKER: [Younghyun Han](#)

ABSTRACT. Predicting anticancer drug responses of

cancer patients is a crucial problem to achieve a higher therapeutic efficacy and to implement precision medicine. It is becoming more feasible to construct a computational model for predicting drug responses since large-scale drug screening data have been accumulated. In this study, we have employed a deep neural network that has feedforward bypass connections to predict anticancer drug responses based on gene expression profiles and drug molecular fingerprints. Drug response data from Genomics of Drug Sensitivity in Cancer (GDSC) database were used. Log(IC50) was used as a prediction target, and this value was normalized for each drug such that all drugs have a same baseline. To divide the whole dataset into a training set and a test set, we undertook two different ways. One is randomly dividing cell lines for each drug into training/test sets, and the other is holding out a subset of cell lines. Our drug response prediction model reached an accuracy of 0.74 Pearson correlation coefficient under first training, test set division setting while 0.49 under second setting which is a higher performance compared to other drug response prediction methods. We also tried to predict missing values from the GDSC database against five MEK1/2 inhibitors and could successfully predict different sensitivities of those cell lines with BRAF mutation although the mutation information has not been used.

Acknowledgements: This work was supported by the National Research Foundation of Korea (NRF) grants funded by the Korea Government, the Ministry of Science, ICT & Future Planning (2015M3A9A7067220, 2014R1A2A1A10052404, and 2013M3A9A7046303). It was also supported by the KAIST Future Systems Healthcare Project from the Ministry of Science, ICT & Future Planning

18:30 [Akram Mohammed](#), [Greyson Biegert](#), [Jiri Adamec](#) and [Tomáš Helíkář](#)

Identification of potential tissue-specific cancer biomarkers and development of cancer versus normal genomic classifiers

SPEAKER: [Akram Mohammed](#)

ABSTRACT. Machine learning techniques for cancer prediction and biomarker discovery can hasten cancer detection and significantly improve prognosis. Recent “OMICS” studies which include a variety of cancer and normal tissue samples along with machine learning approaches have the potential to accelerate such discovery. In this work, 2,175 gene expression samples from nine tissue types were used to identify gene sets whose expression is characteristic of each cancer class. Nine single-tissue, two multi-tissue cancer-versus-normal, and multi-tissue normal classifiers using random forests

classification and ten-fold cross-validation were developed. The single-tissue models -- given a sample of a particular tissue type -- classified the sample as cancer or normal with a testing accuracy between 85.29% and 100%. A multi-tissue bi-class model, which classifies a sample as either cancer or normal achieved a testing accuracy of 97.89%, whereas, a multi-tissue multi-class model, which classifies a sample as cancer versus normal and as a specific tissue type achieved a testing accuracy of 97.43%. A multi-tissue normal model which, given a normal sample of any of the nine tissue, classifies the sample as a particular tissue type achieved a testing accuracy of 97.35%. This study demonstrates the feasibility of predicting the tissue origin of a carcinoma in the context of multiple cancer classes. The machine learning classifiers developed in this study identify potential cancer biomarkers with sensitivity and specificity that exceed those of existing biomarkers. Our tissue-specific biomarkers pointed to metabolic and signaling pathways that are critical to both general and tissue-specific tumor development.

18:30 [Hitomi Kanno, Akinori Nishi, Katsuya Ohbuchi, Hirotaka Kushida, Takashi Matsumoto, Chika Shimobori, Haruo Kuroki, Shigeki Nabeshima, Nozomu Sakurai, Ayako Yachie, Yukiko Matsuoka, Hiroaki Kitano and Masahiro Yamamoto](#)

**Systems biology of multi-herbal formulations:
Addressing condition-dependent prescription selection by comparing pharmacological and compound traits of related formulations**

SPEAKER: [Hitomi Kanno](#)

ABSTRACT. In traditional herbal medicine (THM), different THMs may be prescribed for similar symptoms of a disease depending on the overall condition of the patient. To determine how to select the proper prescription for a patient, it is important to clarify the pharmacological properties of each THM prescription. In traditional Japanese medicine (Kampo), both Maobushisaishinto (MBST) and maoto (MT) prescriptions are commonly used to treat flu-like symptoms, but MBST is specifically used for patients with frailty. Both prescriptions share ephedra herbs (Ephedrae Herba (EH)) as the major ingredient, but their other constituents vary. The differences in the pharmacological properties of these Kampos remain unclear. In this study, we compared the pharmacological and compound traits of MBST and MT by target/non-targeted metabolomics analysis. Pharmacology: we evaluated the effect of MBST and MT on flu-like symptoms by using a rat model of polyI:C-induced inflammation. Both MBST and MT ameliorated the decrease in locomotor activity and proinflammatory cytokines in model rats, but the effects did not differ between the two Kampos.

Targeted metabolomics: we compared changes in endogenous metabolites in rat plasma after MBST and MT treatment. Although both prescriptions affected several metabolic pathways such as amino acid metabolism, we identified metabolites that were affected specifically by only one of the two Kampos. Non-targeted metabolomics: we comprehensively compared the compound and metabolomic profiles of MBST and MT in rat plasma after treatment. Notably, one-quarter of EH-derived compounds were detected only in either Kampo, suggesting that the combination of herbs in each Kampo might affect the extraction and/or absorption of EH compounds. Our extensive pharmacological/compound profiling highlight differences between MBST and MT in chemical composition and in their effects on host metabolism. These analyses will lay the foundation for elucidating the mechanisms of the pharmacological/biological effects of THM.

18:30 [Swati Dubey](#), [Sheela Joshi](#) and [Rajendra Prasad](#)
**Simulation of a Petri net Based Model of the
Menthol Biosynthesis**

SPEAKER: [Swati Dubey](#)

ABSTRACT. Abstract A petri net representation and simulation of biosynthesis of menthol from Geranyl diphosphate (GPP) has been performed with the objective of understating new insights of the structure of this pathway affecting the synthesis of menthol. The model has been validated for its structural and behavioural properties. This understanding is expected to identified reactions that could be experimentally manipulated to enhance the productivity of this medically and commercially important material. Petri nets are a special class of networks, introduced in 1962 by Carl Adam Petri, that provide a convenient language and graphical representation for many kinds of processes in a variety of areas of science and engineering. The petri net model is generated on the basis of literature survey and from the biological databases such as KEGG (Kyoto Encyclopaedia of Genes and Genomes). Petri net is designed through employing the Petri net tool “Hybrid Petri net ICSI simulator”(hisim-1.0)1. The model is simulated and validated against the known experimental data obtained from extensive literature searches. The model posses the basic structural properties of Petri net like PUR, ORD and SC which are necessary for preliminary consistency of the net and its correctness. P-invariant and T-invariant properties were computed with the help of software “Platform Independent Petri net Editor” (Pipe-v4.3)2. The net is utilized to simulate the time (pt) with concentrations of GPP, (-)-Limonene, (+)-pulegone, (-)-Menthone and (-)-Menthol. Dimethylallyl diphosphate (DMAPP) and Isopentenyl diphosphate (IPP) are main precursors

for this biosynthesis. Biological data needed for simulation were obtained from extensive survey of literature. The results are shown graphically, the nature of graphs represent the variation of concentrations with time (pt). Although this metabolic model is basic, it will facilitate a platform for analysing high-throughput data, and it should lead to a more generous understanding of menthol biosynthesis 1
<https://sourceforge.net/projects/hisim/files/hisim/hisim-1.0/> 2 <https://sourceforge.net/projects/pipe2/>

18:30 [Amogh Jalihal](#), [Pavel Kraikivski](#), [Murali T.M.](#) and [John Tyson](#)

Modeling the nutrient signaling network in *Saccharomyces cerevisiae*

SPEAKER: [Amogh Jalihal](#)

ABSTRACT. The regulation of cell growth and division has long been considered a central problem in cell biology. Much work has been done both theoretically and experimentally towards expanding our understanding of the processes of the cell division cycle. However, cellular growth, which is regulated by a complex interplay of nutrient signaling and growth factor signaling pathways remains poorly understood in higher eukaryotes. Specifically, growth in unicellular eukaryotes, in contrast to multicellular eukaryotes, depends only on nutrient availability and not on growth factor signaling. However, the complexity of the interactions in the regulatory network for cellular growth precludes an intuitive understanding of nutrient signaling mediated regulation of cell growth.

Here, we propose an ODE-based dynamical model of the regulatory mechanism governing cell growth in the budding yeast *Saccharomyces cerevisiae*. This model can simulate variations in cellular growth rates as a function of varying macronutrient inputs, namely carbon and nitrogen sources. The model captures the metabolic signaling network composed of components from the TORC1, Snf1, and the Ras-cAMP-PKA pathways, and captures the interactions that impinge on the ribosome biogenesis regulon, which governs the mass growth rate. Previous dynamical models have focused on modeling the responses of pathways involved in specific nutrient responses, or have focused on general stress responses in yeast, involving an overlap with nutritional stress responses. Our model differs from existing efforts in its comprehensiveness in modeling the nutrient response, and its goal of predicting cellular growth rate robustly for a given nutritional input. In the future, we plan on integrating this model of nutrient signaling with the highly successful model of the yeast cell cycle, with the goal of refining the phenotypic predictions made by the cell cycle model.

18:30 [Tongli Zhang](#)

**Understanding the self-renewal, differentiation
and death of intestinal cells**
SPEAKER: [Tongli Zhang](#)

ABSTRACT. After developing from pluripotent embryo stem cells, multipotent intestinal stem cells continuously differentiate into mature functional cells (e.g. Enterocytes, Goblet cells, Enteroendocrine cells and Paneth cells). In presence of oncogenetic mutations, intestinal cells might evolve into cancer cells that are killed during the treatment with chemotherapy drugs. The self-renewal, differentiation and death of intestinal cells are complex dynamical processes that are orchestrated by the molecular control networks in these cells. Previous work has discovered valuable pieces of the molecular control network, but an integrated, systemic understanding of the overall dynamical process remains unknown. Without such an integrated understanding of how the cells normally coordinate their self-renewal and differentiation, it is hard to understand how these processes are disrupted in diseases such as Inflammatory Bowel Disease (IBD) and cancer. Consequently, it is hard to rationally design optimal clinical protocols to treat these diseases. In order to cope with this challenge, we have converted several key pathways into computational models. These models have been constrained with available data reported in the literature, and the novel predictions generated by these models are being tested in intestinal enteroids. Testing of these predictions will indicate how well the system is currently understood and push forward the boundary of our understanding.

18:30 [Gang Yang](#), [Colin Campbell](#) and [Réka Albert](#)
Compensatory interactions to stabilize multiple steady states or mitigate the effects of multiple deregulations in biological networks
SPEAKER: [Gang Yang](#)

ABSTRACT. Complex diseases can be modeled as damage to intra-cellular networks that results in abnormal cell behaviors. Network-based dynamic models such as Boolean models have been employed to model a variety of biological systems including those corresponding to disease. Previous work designed compensatory interactions to stabilize an attractor of a Boolean network after single node damage. We generalize this method to a multi-node damage scenario and to the simultaneous stabilization of multiple steady state attractors. We classify the emergent situations, with a special focus on combinatorial effects, and characterize each class through simulation. We explore how the structural and functional properties of the network affect its resilience and its possible repair scenarios. We demonstrate the method's applicability to two intra-cellular network models relevant to cancer. This work

has implications in designing prevention strategies for complex disease.

18:30 [Weikang Wang](#), [Yi-Jiun Chen](#), [Jingyu Zhang](#), [Min Xu](#) and [Jianhua Xing](#)

Automating cell segmentation and tracking with deep learning algorithms

SPEAKER: [Weikang Wang](#)

ABSTRACT. In single cell time lapse studies cell segmentation and tracking can be time consuming. Using deep learning algorithms, we developed a pipeline that performs automatic segmentation and tracking after learning from a training set of data. We tested the method with data obtained with an E-cad/Vim double-FP-labeled T47D cell line using the CRISPR technique.

18:30 [Pavel Kraikivski](#), [Gengjie Jia](#), [Ilya Mayzus](#), [Andrey Rzhetsky](#) and [John Tyson](#)

Computational Model of Melanoma Cancer

SPEAKER: [Pavel Kraikivski](#)

ABSTRACT. The development of drug resistance by acquired mutations is the main reason that melanoma cancers show only a modest response to single-agent targeted drug therapies. A well-designed combination of drugs that targets multiple molecular pathways can improve overall survival. To understand the molecular mechanisms underlying the development of drug resistance, we have created a comprehensive computational model of the signaling network in melanoma cells and how it responds to systematic perturbations with 90 different drug combinations. For this detailed mathematical model, we use a new modeling framework in which all reactions are classified into three basic types: protein synthesis and degradation ($\rightarrow C \rightarrow$), phosphorylation and de-phosphorylation ($C \leftrightarrow CP$), and binding to activator or inhibitor partners ($C+A \leftrightarrow C:A$). The molecular mechanisms of signaling and cell cycle regulation in melanoma cells have been deduced from protein-protein interaction data obtained by an automated literature extraction method. We used published experimental data on 90 treatments consisting 12 different drugs, each at two different doses, and also different drug-pair combinations. Our initial approach was to train the model to fit experimental data (cell viability or inviability) on 12 drug treatments (either 12 low-dose treatments or 12 high-dose treatments) and compare the model predictions with data on the remaining 78 drug combinations. Trained in this way, the model is successful in explaining ~82% of viability data. We have also tested the model against detailed proteomic data, generating a response map for protein concentrations and an error map for comparison of experimental data with model

predictions. We have parameterized the model using both viability and proteomic data, and we plan to use this version of the model to investigate drug resistance in melanoma and to predict multi-agent targeted therapies that might make it harder for melanoma cells to resist treatment. Our broader goal is to make a generic, customizable model of molecular signaling in cancer cells.

18:30 [Dorjsuren Battogtokh](#), [Shihoko Kojima](#) and [John Tyson](#)

Modeling the Interactions of Sense and Antisense Transcripts in the Mammalian Circadian Clock Network

SPEAKER: [Dorjsuren Battogtokh](#)

ABSTRACT. In recent years, it has become increasingly apparent that antisense transcription play an important role in the regulation of gene expression. Recently, it was reported that the antisense transcript of the mammalian core-clock gene Per2, which we named Per2AS, oscillates with a circadian period and about 12 h phase shift from the peak of expression of Per2 mRNA. In this study, we address the question as to whether Per2AS plays a regulatory role in the mammalian circadian-clock. In particular, we study the potential effects of Per2 and Per2AS interactions on the circadian rhythm in silico, in the context of two hypotheses about how Per2 and Per2AS transcripts mutually interfere with each other's expression. In our 'pre-transcriptional' model, we assume that the process of transcribing Per2AS RNA from the non-coding DNA strand represses the transcription of Per2 mRNA from the coding strand. In our 'post-transcriptional' model, we assume that Per2 and Per2AS transcripts form double stranded RNAs, due to their complementary sequences, and that the duplex RNA is rapidly destroyed. To study these alternative hypotheses, we have modified a mathematical model of the molecular regulatory network of the mammalian circadian clock, originally put forward by Relogio et al [1], by adding new terms describing our proposed hypotheses. Our pre-transcriptional model predicts that Per2-Per2AS interactions can generate alternative modes of circadian oscillations, and we characterize these modes in terms of the amplitude and phase of oscillation of various clock genes. In our post-transcriptional model, antisense overexpression dampens the circadian rhythm. In a model that combines pre- and post-transcriptional controls, the period, amplitude and phase of circadian proteins exhibit non-monotonic dependencies on the rate of expression of Per2AS, presumably as a consequence of the double regulatory functions of Per2AS.

[1]. Relógio A,et al., Tuning the Mammalian Circadian

18:30 [Bronson Weston](#), [John Tyson](#) and [Liwu Li](#)
A Dynamic Model of Granulocyte-Monocyte Progenitor Differentiation
SPEAKER: [Bronson Weston](#)

ABSTRACT. Granulocyte-monocyte progenitor (GMP) cells play a vital role in the immune system as they mature into a variety of white blood cells, including neutrophils and macrophages. In the classical motif of GMP differentiation, GMP cells mature into one of two competing lineages, monocytes or granulocytes, depending on exposure to cytokines such as various types of colony stimulating factors (CSF). Granulocyte-CSF (G-CSF) induces granulopoiesis and macrophage-CSF (M-CSF) induces monopoiesis, while granulocyte macrophage-CSF (GM-CSF) favors monocytic and granulocytic differentiation at low and high concentrations, respectively. Although these differentiation pathways are well documented, the mechanisms behind the diverse behavioral responses of GMP cells to CSFs are not well defined. Using dynamic systems theory we explore the differentiation of GMP cells in response to varying dosages of G-CSF, M-CSF, and GM-CSF. Our model reproduces experimental observations of GM-CSF induced differentiation, and for the first time, we propose a mechanism for this intriguing behavior. Furthermore, we explore the differentiation of a fourth phenotype, monocytic myeloid-derived suppressor cells (M-MDSC), how they fit into the classical motif of GMP differentiation, and how progenitor cells can be primed for M-MDSC differentiation. Finally, we legitimize our model by comparing its results to numerous experiments and make intriguing predictions that should be explored by future experimental studies.

18:30 [Sarah Maddox](#)
Characterizing Phenotypic Heterogeneity in Small Cell Lung Cancer
SPEAKER: [Sarah Maddox](#)

ABSTRACT. Small cell lung cancer (SCLC) is an aggressive tumor type with a strong ability to become resistant to all known treatments and to survive in diverse microenvironments. Proposals to stratify patients based on tumor phenotype have been met with resistance due to unclear clinical relevance, as the “small blue round” SCLC cells are extremely uniform by histopathology, but more recently it has become increasingly understood that SCLC tumors exhibit phenotypic heterogeneity implicated in the aggressiveness of the disease. My central hypothesis is that interactions between these plastic phenotypes

form a functional ecosystem that drives growth and controls the overall response to therapy. The discovery of multiple SCLC phenotypes necessitates further analysis to identify the core SCLC phenotypes and eventually map the phenotypic space.

Consensus clustering and weighted gene co-expression network analysis (WGCNA) applied to transcriptomics data of 53 cell lines and 81 primary human tumors reveal 4 clusters with several gene modules distinguishing them. The clusters found include the neuroendocrine tumor-propagating cell (NE TPC) and supporting mesenchymal-like (ML) phenotypes previously reported in the literature, as well as two novel hybrid phenotypes. We constructed an expanded panel of SCLC candidate markers for single-cell analysis (e.g., by mass cytometry) optimized to distinguish between and ensure broad coverage of these phenotypes. Characterization of the core SCLC phenotypes will contribute substantially to the goal of a global definition of the multi-dimensional variables that drive cooperation between them and support tumor progression and drug evasion.

18:30 [Nicholas Franzese](#), [Anna Ritz](#) and [Adam Groce](#)
Practicality and Relaxation of Shortest Hyperpath Analysis on Biological Networks
SPEAKER: [Nicholas Franzese](#)

ABSTRACT. Networks of biological molecules are commonly analyzed using graph-theoretic techniques. Recent studies have implicated directed hypergraphs (a generalization of the standard graph that makes use of the hyperedge, which expresses a relationship between two or more vertices) as an additional modeling tool for biological networks with greater inferential utility, at the cost of computational efficiency for certain algorithms. For example, finding the shortest hyperpath (a sub-hypergraph joining a source and target according to a restrictive definition of connectivity) between a pair of nodes is an NP-hard problem, though an existing algorithm tends to solve it quickly on protein interaction hypergraphs.

Topological analysis on two protein interaction hypergraphs revealed that both were divided up into tiny regions of hyperpath reachability. Benchmarking of the shortest hyperpath algorithm on these hypergraphs demonstrated robustly short runtimes. In contrast, randomly-generated hypergraphs with a denser distribution of hyperedges exhibited longer runtimes consistent with the expectation of NP-hardness. From these preliminary results we concluded that simple sparsity of biological network hypergraphs is a major contributor to the reasonable runtime phenomenon.

Building on these results we constructed an

augmented version of the shortest hyperpath algorithm (implemented as a mixed integer linear program). The method, called the cheating hyperpath algorithm, iteratively relaxes the connectivity constraints of the shortest hyperpath algorithm, expanding the space of feasible source target pairs beyond the small fragments observed in my preliminary results. With this algorithm we replicated earlier demonstrations of the utility of hyperpath-based analysis through automated capture of the canonical Wnt pathway. For example, the cheating hyperpath from WNT3A to β-catenin contained 12 nodes and 5 hyperedges, requiring 3 cheats. Additionally, we constructed a scenario which demonstrates the cheating hyperpath algorithm's novel capabilities for examining signaling crosstalk. These results highlight the promise of hypergraph-theoretic methodologies as a mode of biological network analysis.

18:30 [Geena Ildefonso](#), [Michael Irvin](#) and [Carlos Lopez](#)
Building a Mechanistic Understanding of Cell Death or Survival Decisions in L929 Cells
SPEAKER: [Geena Ildefonso](#)

ABSTRACT. Cells constantly process extracellular stimuli that can lead to multiple phenotypic outcomes. In this work, we study how L929 cells, stimulated with TNF_α, execute death (programmed necroptosis) or survival through the Nuclear Factor kappa-B (NF-_B) signaling network. Although the NF-_B pro-survival network and the necroptosis network are typically studied in isolation, recent work by the Hoffmann lab has shown evidence that crosstalk between the networks exists. A mechanistic understanding of this crosstalk would thus provide insights about cellular intracellular communication that employs a complex system of interactions to achieve alternate outcomes. To understand the complex interactions that lead to TNF stimulation, we build and calibrate mathematical models of complex biochemical systems, as a tool to probe molecular interactions and mechanisms, outside the reach of current experimental technologies. In this work, we recapitulate the NF-_{κB} model by, Hoffmann et al., a set of ordinary differential equations using mass-action kinetics, in PySB to ensure that our implementation recapitulates key aspects of NF-_{κB} signaling. We then extend this model with a necroptosis execution module in PySB that extends the original NF-_{κB} model to enable the exploration of programmed necroptosis, through the regulation of anti-apoptotic signals. We also intend to link the model with other models of necroptosis to better understand cell fate outcomes in cancers.

18:30 [Carlos Contreras](#), [Gustavo Carrero](#) and [Gerda de Vries](#)
Understanding the effect of radiation on the cell

cycle through mathematical modelling

SPEAKER: [Carlos Contreras](#)

ABSTRACT. The cell cycle comprises a chain of events that results in the division of a cell into two daughter cells. It is carefully regulated by a complex network of control mechanisms including cyclin-Cdk interaction, DNA replication and checkpoints. In particular, the G2 checkpoint checks the integrity of the DNA before proceeding to mitosis. In the presence of DNA damage, the cell cycle is arrested in this checkpoint until the damage is repaired. Failure to activate or maintain this checkpoint causes genome instability and, in some cases, cancer cells. This is critically important in radiation therapy since it has been shown that G2 checkpoint activation is compromised for low doses of radiation [1, 2]. Here, we study the effect of radiation on the cell cycle through a mathematical model based on a Minimal Cdk Network [3]. In our modified version of the model, we include a DNA damage pathway and study its effect on the cell cycle (represented by a stable limit cycle). We identify the G2 checkpoint activation in the cell cycle with a saddle-node on an invariant circle (SNIC) bifurcation. For a small dose of radiation below a threshold, we observe that the period of the limit cycle increases (which corresponds to a delay in the progression into M-phase); for higher dose of radiation above the threshold, we observe a loss of the limit cycle and the appearance of a node and a saddle (corresponding to the activation of the checkpoint). We also observe that the G2 checkpoint, determined by the saddle point, is located right before mitosis and depends dynamically on the amount of radiation. Our results provide a foundation for understanding many phenomena observed in low-dose radiation, including hyper-radiosensitivity and increased radioresistance (HRS/IRR) phenomenon observed in the study of survival fraction after radiation.

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18:30 [Debraj Ghose](#), [Timothy Elston](#) and [Daniel Lew](#)

Chemotropism in yeast

SPEAKER: [Debraj Ghose](#)

ABSTRACT. Eukaryotic single cells such as migrating

cancer cells, developing neurons, or mating yeast move (chemotaxis) or grow (chemotropism) in a specific direction by using a chemical gradient for directional reference. Existing models for how eukaryotic cells sense chemical gradients assume cells compare concentrations of ligand-bound receptors across the cell surface to infer the gradient. However, our studies, using yeast chemotropic mating as a model, suggest that cells may sense a chemical gradient with a sensitive front that is mobile on the cell cortex. We have modeled the dynamics of this moving sensitive front with stochastically perturbed reaction-diffusion equations.

In this study, we show that an *in silico* cell based on this computational model is capable of sensing pheromone gradients. However, the model cannot sense shallow gradients as well as yeast in *in vivo* experiments. When we incorporate the effects of an additional pathway recently implicated in gradient sensing in yeast into our mathematical model, the model's ability to track pheromone gradients improves significantly. Furthermore, we experimentally demonstrate that the dynamics of a sensitive front that emerge from genetic perturbations recapitulate the dynamics generated by the mathematical model. In summary, we propose a mechanistic basis for a novel pathway necessary for tracking chemical gradients accurately.

18:30 [Ciaran Welsh](#) and [Daryl Shanley](#)

Towards a Computational Model of the Dermal Extracellular Matrix in Ageing

SPEAKER: [Ciaran Welsh](#)

ABSTRACT. The dermal extracellular matrix (ECM) plays a vital role in providing tensile strength, elasticity and hydration to the skin. The ECM is primarily composed of type 1 and 3 collagens but also consists of an array of various other components, the abundance of which optimizes skin function. With age, this balance is driven away from normal homeostasis resulting in less and disorganized collagen, reduced strength and elasticity and the other characteristics of skin ageing. In this study, time course expression profiles (12 time points over 96h, n=6) were collected from three cell lines (neonatal human dermal fibroblasts [HDFs], irradiation induced senescent HDFs [IR] and adult HDFs [56 years +], n=3 per cell line) in response to transforming growth factor beta (TGF β) or control using both Affymetrix microarray and high throughput (WaferGen) PCR technology. Here we report on the analysis of a subset of this data (pilot data) which has been used to establish computational methods to extract meaningful information. We apply an integrated top-down and bottom-up systems biology methods using the '-omic' level data to highlight differences between

young, IR and adult cell lines with respect to the fibroblast TGF β response and ODE modelling strategies to build dynamic models of these differences. We aim to identify novel means of treating the aged phenotype.

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08:00-17:00 Session : Registration

LOCATION: Williamsburg Room

08:30-10:30 Session 14: Wednesday Moring

CHAIR: [Jing Chen](#)

LOCATION: Colonial Hall

08:30 [Keren Lasker](#)

TBA

SPEAKER: [Keren Lasker](#)

09:00 [Jianhua Xing](#)

Multi-Objective Optimization in Biology and Biomedicine

SPEAKER: [Jianhua Xing](#)

ABSTRACT. Multiple-objective optimization is common in biological systems. Some of these objectives are incompatible, thus tradeoffs are necessary. living organisms are constantly under selection pressure to maximize their fitness to the environment through optimizing multiple objectives such as growth rate and resistance to environmental fluctuations. In this talk I will focus on two problems that we worked on recently.

In the mammalian olfactory system, each sensory neuron stochastically expresses one and only one out of up to thousands of olfactory receptor (OR) gene alleles; at the organism level, the types of expressed ORs need to be maximized. This Nobel-prize winning observation raises one of the most intriguing puzzles in neurobiology that remains elusive after several decades of intensive investigations: how can both monoallelic and diverse expression of OR be ensured at the same time? Our theoretical studies unraveled how cells achieve these objectives through simple physical principles. The model makes extensive testable predictions. Some are so counterintuitive that the corresponding experimental results, published before the model, received great skepticism in the field, and are predicted by the model with mechanistic explanation.

Acute Kidney Injury (AKI) affects ~13.3 million patients, and is associated with ~1.7 million death globally each year. Even recovered from AKI patients have much higher risk to develop chronic kidney diseases (CKD). About 13% of the population in US suffer from CKD, and the disease eventually leads to end-stage renal disease (ESRD). There is no effective treatment for either AKI or CKD. AKI and CKD are traditionally two separate fields of study. Using combined mathematical modeling and mouse model studies, we showed that the transition from AKI to CKD comes from evolutionary compromise, and resolved some decades-long debate. Furthermore, our studies showed that targeting the recovering dynamics after AKI can potentially improve the repair process without increasing the risk of CKD.

09:30 [Coffee Break](#)

Wednesday Coffee Break

SPEAKER: [Coffee Break](#)

10:00 [Thomas Hofer](#)

Newly Born Cancer Cells Escape Chemotherapeutic Drug

SPEAKER: [Thomas Hofer](#)

ABSTRACT. While many tumors initially respond to chemotherapy, regrowth of surviving cells compromises treatment efficacy in the long-term. The cell biological basis of this regrowth is not understood. Here, we characterize the response of individual, patient-derived neuroblastoma cells driven by the prominent oncogene MYC to the first-line chemotherapy, doxorubicin. Combining live-cell imaging, cell-cycle-resolved transcriptomics, and mathematical modeling, we demonstrate that a cell's treatment response is dictated by its expression level of MYC and its cell-cycle position prior to treatment. All Low-MYC cells enter therapy-induced senescence. High-MYC cells, by contrast, disable their bistable cell-cycle checkpoints, forcing renewed proliferation despite treatment-induced DNA damage. After treatment, the viability of High-MYC cells depends on their cell cycle position during treatment: newborn cells promptly halt in G₁ phase, repair DNA damage, and form regrowing clones; all other cells show protracted DNA repair and ultimately die. These findings demonstrate that fast-proliferating tumor cells may resist cytotoxic treatment non-genetically, by arresting within a favorable window of the cell cycle.

10:30-12:30 Session 15A: Parallel Session IV a: Developmental Dynamics and Control

CHAIR: [Thomas Hoefer](#)

LOCATION: Brush Mountain A & B

10:30 [Dola Sengupta](#) and [Sandip Kar](#)

Deciphering the dynamical origin of mixed population during neural stem cell development

SPEAKER: [Dola Sengupta](#)

ABSTRACT. Neural stem cells (NSC's) often give rise to mixed population of cells during differentiation. However, the dynamical origin of these mixed states is poorly understood. In this article, our mathematical modeling study demonstrates that the bone morphogenetic protein 2 (BMP2) driven differential differentiation dynamics of NSC's in central and peripheral nervous systems essentially function through two distinct bi-stable switches that are mutually interconnected. Stochastic simulations of the model reveal that the mixed population originates due to the existence of these bi-stable switching regulations while the maintenance of such mixed states depends on the level of stochastic fluctuations of the system. Importantly, the model predicts that by individually altering the expression level of key regulatory proteins, the NSC's can be converted entirely to a preferred phenotype for BMP2 doses that earlier resulted into mixed population. Our findings show that efficient neuronal regeneration can be achieved by systematically maneuvering the differentiation dynamics.

10:50 [Tian Hong](#), [Chung-Jung Li](#), [Qing Nie](#) and [Jun-An Chen](#)

The dual role of microRNA in boundary formation of the spinal cord

SPEAKER: [Tian Hong](#)

ABSTRACT. The initial rostrocaudal patterning of the neural tube leads to differential expression of Hox genes that contribute to the specification of motor neuron (MN) subtype identity. Although several Hox mRNAs are expressed in progenitors in a noisy manner, these Hox proteins are not expressed in the progenitors and only become detectable in postmitotic MNs. MicroRNA biogenesis impairment leads to precocious expression and propagates the noise of Hoxa5

at the protein level, resulting in an imprecise Hoxa5-Hoxc8 boundary. Using *in silico* simulations, we uncovered two feed-forward Hox-miRNA loops accounting for the precocious and noisy Hoxa5 expression, as well as an ill-defined boundary phenotype in Dicer mutants. In addition, we identified mir-27 as a major regulator coordinating the temporal delay and the spatial boundary of Hox protein expression. Using more detailed computational analysis, we further predict that the Hox-miRNA circuit underlies a bistable switch with delayed Hoxa5 expression, and that the bistability and the delay synergistically enables a beneficial effect of Hoxa5 transcriptional noise in sharpening of the Hoxa5-Hoxc8 boundary. This intracellular noise contributes to the attenuation of the fluctuations in extracellular morphogens. Therefore, the microRNA can both control and take advantage of the Hoxa5 expression noise. Our results demonstrate a novel mechanism for Hox-miRNA circuit to confer robustness to both individual MN identities and the tissue boundary.

11:10 [Lei Zhang](#) and [Feng Liu](#)

Exploring the inhibitory effect of membrane tension on cell polarization

SPEAKER: [Lei Zhang](#)

ABSTRACT. Cell polarization toward an attractant is influenced by both physical and chemical factors. Most existing mathematical models are based on reaction-diffusion systems and only focus on the chemical process occurring during cell polarization. However, membrane tension has been shown to act as a long-range inhibitor of cell polarization. Here, we present a cell polarization model incorporating the interplay between Rac GTPase, filamentous actin (F-actin), and cell membrane tension. We further test the predictions of this model by performing single cell measurements of the spontaneous polarization of cancer stem cells (CSCs) and non-stem cancer cells (NSCCs), as the former have lower cell membrane tension. Based on both our model and the experimental results, cell polarization is more sensitive to stimuli under low membrane tension, and high membrane tension improves the robustness and stability of cell polarization such that polarization persists under random perturbations. Furthermore, our simulations are the first to recapitulate the experimental results described by Houk et al., revealing that aspiration (elevation of tension) and release (reduction of tension) result in a decrease in and recovery of the activity of Rac-GTP, respectively, and that the relaxation of tension induces new polarity of the cell body when a cell with the pseudopod-neck-body morphology is severed.

11:30 [Jian-Geng Chiou](#), [Timothy Elston](#), [Thomas Witelski](#), [David Schaeffer](#) and [Daniel Lew](#)

Principles that govern competition or co-existence in Rho-GTPase driven polarization

SPEAKER: [Jian-Geng Chiou](#)

ABSTRACT. Rho-GTPases are master regulators of polarity establishment and cell morphology in many eukaryotes. Upon receiving relevant signals, Rho-GTPases become concentrated in clusters at the cell cortex, from where they regulate the cytoskeleton to influence cell behavior. The biochemical mechanisms underlying such clustering include common features such as positive feedback and differential mobility of membrane-associated and cytoplasmic components. The specific functionalities of different cell types require the generation of either one (e.g. the front of a migrating cell) or several clusters (e.g. multiple dendrites of a neuron), but the mechanistic basis for uni-polar or multi-polar outcomes is unclear. Insights into the design principles of Rho-GTPase circuits were provided by simple two-variable reaction-diffusion models that capture essential features of GTPase biochemistry. Here, we use

such models to show that when more than one GTPase cluster forms, the core polarity circuit enforces competition between the clusters to yield a uni-polar outcome. However, the efficiency of competition is determined by parameter values in a switch-like manner, with some parameter choices dampening competition to the point that multiple domains can persist on biologically relevant timescales. We derive a “saturation rule” that governs the timescale of competition, and hence whether the system will generate uni-polar or multi-polar outcomes. Our theory suggests that the saturation rule is an fundamental property of the Rho-GTPase polarity machinery, regardless of the specific feedback mechanism.

11:50 [Yunseong Kim](#), [Jung-Min Yang](#) and [Kwang-Hyun Cho](#)
Identifying synergistic control targets of a biological network based on a merged state transition map
SPEAKER: [Yunseong Kim](#)

ABSTRACT. Biological networks are complicatedly wired and therefore we often need more than one control targets to change their attractor state into a desired one. Although various control target selection methods, such as feedback vertex sets (FVS) or minimum dominating sets (MDS) were suggested, the resulting control targets do not indicate synergistic drug targets. The main reason is that such methods are using only the information of network topology. It is true that the steady state or the controllability of a network heavily depends on the network topology, but the synergistic effects are primarily caused by complex network dynamics which are not solely determined by the network topology. Thus, we need to develop a new control strategy that can identify useful synergistic control target pairs based on both topology and dynamics of the network. For this purpose, we have developed a novel method of identifying synergistic control targets by merging the state transition maps before and after virtual perturbations of the network nodes. We also developed a scoring algorithm to evaluate the synergistic effect of each node perturbation. The proposed method compares the average activities and state alteration numbers of network nodes between the desired direction and the opposite direction of the state transition flow in the merged transition map. The scores are weighted based on the phenotypic information according to the attractor classification criteria of the network. We applied the proposed method to published Boolean network models of biological networks and confirmed that our method can identify synergistic drug targets. In addition, by visualizing the merged state transition map and analyzing the state transition flow upon it, we can further reveal the hidden mechanisms of the identified synergistic drug pairs.

Acknowledgements: This work was supported by the National Research Foundation of Korea (NRF) grants funded by the Korea Government, the Ministry of Science, ICT & Future Planning (2015M3A9A7067220, 2014R1A2A1A10052404, and 2013M3A9A7046303). It was also supported by the KAIST Grand Challenge 30 Project grant.

10:30-12:30 Session 15B: Parallel Session IV b: Cell Decision Making I

CHAIR: [Matteo Barberis](#)
LOCATION: Room 342 in Squires

10:30 [Gabriel Neurohr](#), [Rachel Terry](#), [Bela Novak](#), [John Tyson](#) and [Angelika Amon](#)
Cell size homeostasis is critical for maintaining a permissive DNA:Cytoplasm ratio
SPEAKER: [Gabriel Neurohr](#)

ABSTRACT. Cell size in multicellular organisms can vary across several orders of magnitude between different cell types. Even in the unicellular budding yeast, cell volume ranges between 10-200 μm^3 ,

depending on developmental stage, environmental conditions and age. However, in a given cell type or a specific environment all cells are of the same size. This indicates that size is critical for cell function. How cell size influences cell physiology is not clear.

We used budding yeast to address this question. Using a reversible cell cycle arrest we generated largely oversized cells. Consistent with previous observations in *S. pombe*, mRNA and total protein levels do not scale with cell volume once cells exceed a critical size, the cytoplasm of oversized cells is therefore diluted.

Increased cell size interfered with basic cellular processes such as cell surface receptor signaling and transcription induction. In addition oversized cells proliferated poorly when released from the cell cycle block. Increasing ploidy or reducing proteasome activity restored size associated signaling-, transcription- and proliferation defects in oversized cells. This shows that dilution of the cytoplasm is detrimental for cell function. We are currently generating *in silico* models of cell cycle progression in differently sized cells to understand how dilution of critical components affects timing and fidelity of a complex process such as cell cycle progression.

10:50 [Toru Matsu-Ura](#), [Andrey Dovzhenok](#), [Sookkyung Lim](#), [Sean Moore](#) and [Christian Hong](#)

Intercellular Coupling of the Cell Cycle and Circadian Clock in Adult Stem Cell Culture

SPEAKER: [Toru Matsu-Ura](#)

ABSTRACT. Coupled oscillators generate diverse behaviors in a variety of organisms. In autonomous cell systems such as fibroblasts, the circadian clock and the cell cycle are coupled intracellularly with a 1:1 ratio. However, the coupling of clock and mitosis is putatively more complex in heterogeneous, multicellular systems and tissues. Here, we demonstrate dynamic Wnt-mediated intercellular coupling between cell cycle and circadian clock in primary 3D cultures of murine intestinal organoids (enteroids), which is a complex organotypic structures containing intestinal stem cells (ISC), progenitor cells (PC), and differentiated cells (DC).

Remarkably, populations of enteroids show circadian clock-dependent synchronized cell division cycles with a period of ~12-h. In contrast, cell cycle measurements from single cells demonstrate a heterogeneous, multimodal distribution of cell cycle times (CCT) with an average period of ~19-h, apparently inconsistent with the population data. To resolve this discrepancy, we developed mathematical model assumed that enteroids consist of ISC and PCs as proliferating cells with CCTs of 16 and 26-h, respectively, in the absence of circadian connections. With stochastic simulations, we find that circadian rhythms regulate the timing of cell divisions in a heterogeneous population that collectively emerge as synchronized 12-h cell division cycles. Furthermore, when these cells are segregated into ISC and PCs, we uncovered 1:1 and 1:2 coupling ratios in ISC and PCs, respectively, in both simulation and experiment. We further observe lack of circadian oscillations in ISC and PCs, indicating an intercellular signal from DCs mediates circadian clock-dependent synchronized cell division cycles. Simulation and experimental results indicate a key role of circadian rhythms in regulating synchronized divisions of ISC and PCs via intercellular Wnt signaling.

11:10 [Michael Flossdorf](#), [Veit Buchholz](#), [Yi-Li Cho](#), [Lorenz Kretschmer](#) and [Thomas Höfer](#)

Dynamics of T cell memory generation inferred from single cell fate mapping *in vivo*

SPEAKER: [Michael Flossdorf](#)

ABSTRACT. Adaptive immune responses to infection or cancer rely on coordinated programs of cell proliferation and differentiation. Upon infection, naive, antigen-specific T cells expand vigorously and give rise to short-lived effector and long-lived memory cells. Conflicting models have been proposed that suggest either of these subsets to be a precursor of the other; how this subset diversification is regulated by external stimuli like T cell receptor (TCR) avidity, antigen availability or inflammation is largely unknown. Here we show that single cell fate mapping data, interrogated by stochastic population modeling and large-scale model discrimination, are surprisingly informative on both the topology and regulation of differentiation pathways. We find that the phenotypic diversity of T cell responses is generated through stochastic linear cell-fate progression: Naive T cells give rise to slowly dividing memory precursor cells from which rapidly dividing short-lived subsets emerge. This process is modulated but not determined by TCR avidity, which we find to affect the probability with which stochastic division and differentiation events occur. For polyclonal T cell responses, our mathematical model provides a mechanistic explanation for the longstanding observation that high avidity T cell clones within a population of responding T cells only become dominant throughout repetitive immunizations. Proliferation of the T cells is furthermore strongly dependent on both inflammatory signals and continuous stimulation of the TCR. However, we find that the expansion of (central) memory precursors is more dependent on TCR stimuli than the other subsets. Taken together, our mathematical model begins to provide a quantitative picture of the developmental program of T cells during an immune response. Improvements in the quantitative understanding of this process will have implications for immunotherapy and the design of effective vaccines.

11:30 [Frank S. Heldt](#), [Reece Lunstone](#), [John J. Tyson](#) and [Bela Novak](#)
Dilution of the cell cycle inhibitor Whi5 alone cannot account for size control in budding yeast
SPEAKER: [Frank S. Heldt](#)

ABSTRACT. Proliferating cells tie cell division to growth in order to maintain their size within an optimal range. In budding yeast (*S. cerevisiae*), size control occurs at START, the point of irreversible commitment to the cell cycle, which can only be passed once a certain critical size is reached. However, how exactly cells measure their size and relay this information to the cell cycle remains controversial.

Here, we present two mechanistically based, mathematical models of size control in yeast cells, in order to assess a recent suggestion that cell growth controls entry into the cell cycle by diluting an inhibitor of START, Whi5. We show that this ‘inhibitor dilution’ model is consistent with most experimental observations but critically fails to account for the size of diploid cells that harbour only one copy of the WHI5 gene. We then propose an alternative model, where Whi5 and its opposing activator, Cln3, are titrated against a constant number of sites on the genome occupied by the transcription factor SBF. This ‘titration of nuclear sites’ model captures all of the above data including the Whi5-independent increase in size of diploid cells. We also show that Whi5 dilution supports the START transition in this model but is not essential for proper cell size control. In summary, our modelling study suggests that the titration of nuclear sites is the dominant size-control mechanism in budding yeast. Because of the functional analogies between Cln3-Whi5-SBF in budding yeast and CycD-RB-E2F in mammalian cells, the titration of nuclear sites may be a conserved scenario in higher eukaryotes.

11:50 [Xili Liu](#), [Seungeun Oh](#) and [Marc Kirschner](#)

Proliferating mammalian cells modulate growth rate to reduce size variability

SPEAKER: [Xili Liu](#)

ABSTRACT. In proliferating cells, variability in cell size can rise from variability in growth rate, cell cycle length and the ratio between the two progeny cells. During recent years, the understanding about how single cell organisms restrict their size variability for the stable size distribution has built up rapidly. However, the mechanism of size control in proliferating mammalian cells remain largely unknown due to the lack of practical and accurate cell size measurement.

Quantitative Phase Microscopy (QPM) is one of the gold standards to measure cell dry mass, whose sensitivity can be as low as 5 pg or 1% of the total cell dry mass. Here we turned this state-of-the-art technique into a robust and handy method to monitor the change of cell mass, with the throughput up to 1000 cells per minute and in different growth conditions. Using QPM, we observed the direct evidence of growth rate adjustment to reduce size variability in proliferating mammalian cells at two specific cell cycle stages. In late G1 and middle S phases, the correlation between cell mass and growth rate changes from positive to negative, thus the difference between large and small cells decreases. In the future, we will integrate the cell mass and growth rate quantification with other screenings to investigate the underlying mechanisms of growth rate dependent cell size control.

12:10 [Zhengda Li](#), [Ye Guan](#) and [Qiong Yang](#)

Incoherent inputs enhance robustness of biological oscillators

SPEAKER: [Qiong Yang](#)

ABSTRACT. Robustness is a critical ability of biological oscillators to function in environmental perturbations. Although central architectures that support robust oscillations have been extensively studied, networks containing the same core vary drastically in their potential to oscillate, and it remains elusive what peripheral modifications to the core contribute to the large variation. We computationally generate a complete atlas of two- and three-node oscillators, to systematically analyze the association between network structures and robustness. We found that, while certain core topologies are essential for producing a robust oscillator, local structures can substantially modulate the degree of the robustness. Most strikingly, local nodes receiving incoherent (positive plus negative) or coherent (both positive or both negative) inputs promote or attenuate the overall network robustness significantly in an additive manner. These motifs are validated in larger-scale networks. Additionally, we found that incoherent inputs are enriched in almost all known natural and synthetic oscillators, suggesting that incoherent inputs may be a generalizable design principle that promotes oscillatory robustness. Our findings underscore the importance of local modifications besides robust cores, which explain why auxiliary structures not required for oscillation are evolutionarily conserved, and further suggest simple ways to evolve or design robust oscillators. Experimentally, we use microfluidics and fluorescence microscopy to investigate how network structures are linked to the essential functions of early embryonic cell cycles.

10:30-12:30 Session 15C: Parallel Session IV c: NeuroScience

CHAIR: [Mike Bowers](#)

LOCATION: Old Dominion Ballroom

10:30 [Uiryong Kang](#), [Byeongwook Lee](#), [Hongjun Chang](#) and [Kwang-Hyun Cho](#)

Increasing the network communicability of a damaged brain network for rehabilitation

SPEAKER: [Uiryong Kang](#)

ABSTRACT. The brain has been studied as a complex networked system using various global and local network measures which can describe different aspects of the brain network. Among them, communicability is an extended measure of information flow by considering multiple paths between node pairs. The significance of communicability has been validated by many researchers studying the organizational principles of the brain, and also by clinicians dealing with lesion-like brain disorders such as stroke and multiple sclerosis. However, there is no study about the way of increasing communicability in damaged brain networks, which might provide us with a clue for brain rehabilitation. To tackle this problem, we have extracted structural brain networks of 40 normal adults from WU-Minn HCP's T1w and DTI image data. We then simulated brain disorders by attenuating or deleting some of the edges in the network. We further tested different edge addition strategies to find a method for restoring the communicability. As a result, we found that the optimal edge addition strategies depend on network attack methods. Among those, we found that there is a robust strategy for restoring the communicability regardless of the state of a damaged network. Our study provides a novel insight into the rehabilitation strategy for damaged brain networks in view of the network communicability.

10:50 [Byeongwook Lee](#), [Uiryong Kang](#), [Hongjun Chang](#) and [Cho Kwang-Hyun](#)

The minimum dominating sets in a brain network critically determine the efficiency of local communication of the network

SPEAKER: [Byeongwook Lee](#)

ABSTRACT. Recently, the focus of systems neuroscience shifted to the determination of brain regions that allow the control of a whole-brain structural network. Finding the minimum dominating sets (MDSets) of regions, which potentially provide efficient sources of influence and information dispersal, can be a starting point for establishing a control strategy of the brain network. An intriguing question then arises as to whether such sets of regions have any important functional characteristics. In this study, we have investigated the MDSets of regions in the whole-brain structural network of human. In general, high-degree regions are more likely to be dominator nodes than low-degree regions, but, unexpectedly, the MDSets of regions include relatively low-degree regions and are minimally overlapped with rich-club regions. We further investigated the role of the MDSets of regions through network attack simulation and compared the result with that of the attack on the rich-club regions. We found that attacking the rich-club regions significantly decreases the global efficiency of the network while attacking the MDSets of regions significantly decreases the local efficiency of the network. Our study indicates that MDSets of regions might play a crucial role in local communication of the whole-brain structural network.

11:10 [Gianluca Selvaggio](#) and [Robert Pearlstein](#)

Using action potential simulations to explore the possible cause-effect relationships between gain and loss of cardiac ion channel function and generation of proarrhythmic early afterdepolarizations

SPEAKER: [Gianluca Selvaggio](#)

ABSTRACT. Cardiac action potentials (APs) are generated by the continuous dynamic balance between inward and outward voltage-gated ion channel currents. Gain or loss of channel function results in current imbalances, translating to AP prolongation (balance tipped in the inward) or shortening (balance tipped outward). Early

afterdepolarizations (EADs), a known triggers for torsade de pointes arrhythmia, occur at a threshold increase in net inward current (1,2). Mild reduction in either or both of the outward IK1 and IKr currents due to mutations, results in higher susceptibility to EADs (3,4). We used the O'Hara-Rudy model of the undiseased human heart (5) to study the detailed mechanism by which EADs are generated in midmyocardial cells. As typical of dynamic instabilities, EADs result from a cascade of precipitating events. The AP transitions from a quasi- to a fully unstable state happens abruptly, for a particular value of current imbalance. Careful manipulation of the model was required to resolve these events, including complete abrogation of IK1, combined with mild hERG blockade. The results of our simulations suggest that EAD genesis is initiated by the spontaneous loss of IK1 at a critical inward current imbalance, due to prolongation of the AP at -50 mV (appearing as a shoulder in the waveform). IK1 plays a critical role in resetting the initial conditions of the system prior to the start of each AP cycle. Wherein the loss of this current results in: 1) abnormal buildup of Cav1.2 channels in the fast-inactivated state; 2) increase of the recovery-induced ICaL; and 3) a vicious circle of error propagation, consisting of abnormal Ca²⁺ release from internal stores, CAMKII activation, Cav1.2 phosphorylation, eventually increasing further Ca²⁺ influx. The accumulation of Ca²⁺, together with an increasing diastolic inward current generated by the Na⁺-Ca²⁺ exchanger, progressively moves the cell toward a more depolarized pro-arrhythmic state.

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11:30 Sebastian Sten, Karin Lundengård, Fredrik Elinder, Maria Engström and Gunnar Cedersund

Multi-level modelling for a new physiologically based interpretation of fMRI data

SPEAKER: Sebastian Sten

ABSTRACT. Functional Magnetic Resonance Imaging (fMRI) indirectly measures brain activity by registering changes in oxygen content that occur in response to neuronal activity. fMRI is being used in thousands of research articles and clinics each year, and is one of the two most common measurement techniques for recording brain activity. Despite this common usage, classical analysis of fMRI data is quite simplistic: it essentially consists of a correlation analysis with a pre-defined shape, even though it is known that the fMRI signal can behave very differently in different parts of the brain. This prompts development of new ways to interpret fMRI data that are more firmly based on our mechanistic understanding of how the

signal is produced.

We have developed a mechanistic model based on ordinary differential equations that describes the intracellular signalling that connects neuronal glutamate and GABA release with vascular and metabolic mechanisms controlling brain oxygen level; this constitutes the previously unmodelled part of the basis for the fMRI signal. We have thereafter combined this model with the previously developed Balloon model, which describes the dynamic interplay between blood volume and flow. The combined model can describe fMRI data from several different clinical studies, featuring different types of response shapes in different parts of the brain, and can describe both estimation data used for parameter fitting, and independent validation data, used for model testing. Some of the key mechanisms in the model has also been tested using optogenetic experiments, where specific parts of the brain can be stimulated directly using light. Finally, using advanced uncertainty analysis, we have also characterized features in the model that can be uniquely identified from ordinary patient data, and that thus can serve as a new type of biologically based biomarkers, which can be used for patient stratification and diagnosis in a clinical setting.

11:50 [Hongjun Chang](#), [Byeongwook Lee](#), [Uiryong Kang](#) and [Kwang-Hyun Cho](#)

A study on frequency-dependent state transition patterns in brain networks using energy landscape analysis

SPEAKER: [Hongjun Chang](#)

ABSTRACT. The brain is a large complex network where various cognitive functions are embedded. To understand its dynamics, a system-level analysis is required. Resting-state recordings of the brain such as MEG or fMRI have been used as a common tool for studying resting-state brain networks and they show time-varying interactions across brain regions for specific cognitive functions. So far, Pearson's correlation coefficient has been primarily used to measure the inter-regional relationships, but complex interactions among multiple brain regions cannot be fully quantified by this due to the assumption of the Pearson's correlation that the pairwise regional interactions are independent of each other. Hence, in this study, we introduced the maximum entropy model based on resting-state MEG recordings to characterize the complex interdependent interactions between regions. Using this model, we further carried out energy landscape analysis to find out distinct resting-state dynamics for eight different frequency bands. We could observe state transitions upon each frequency-dependent landscape and found different dynamic activity patterns for each specific resting-state network. We also found local minima of each landscape and identified regions overlapped with the minima of multiple landscapes, which indicates control target regions for cross-frequency coupling. In summary, our study provides a novel insight into the brain resting-state dynamics from energy landscape analysis of frequency-dependent brain regional activities obtained by high temporal resolution of MEG.

12:30-14:00 Session : Wednesday Lunch

LOCATION: Commonwealth Ballroom

14:00-19:00 Session : Free Time and Activities

LOCATION: Alumni Mall Entrance

19:00-21:00 Session : Conference Dinner

CHAIR: [Young Cao](#)

LOCATION: The Inn at Virginia Tech - Latham Ballroom

ICSB 2017: INTERNATIONAL CONFERENCE ON SYSTEMS BIOLOGY 2017

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PROGRAM FOR THURSDAY, AUGUST 10TH

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08:00-10:00 Session : Registration

LOCATION: Williamsburg Room

08:30-10:30 Session 16: Thursday Morning

CHAIR: [*Madhav Marathe*](#)

LOCATION: Colonial Hall

08:30 [*Chris Barrett*](#)

TBA

SPEAKER: [*Chris Barrett*](#)

09:00 [*Nick Buchler*](#)

Hijacking and rewiring a G1/S regulatory network in Fungi

SPEAKER: [*Nick Buchler*](#)

ABSTRACT. Although cell cycle control is a conserved and essential process, some core animal and fungal cell cycle regulators are not homologous (e.g. E2F and SBF). We recently showed that evolution along the fungal lineage was punctuated by the early acquisition and entrainment of the SBF transcription factor, a protein with homology to a domain commonly found in DNA viruses (Medina et al, 2016).

Ancestral SBF likely hijacked cell cycle control by binding cis-regulatory elements targeted by E2F and activating transcription of G1/S genes to drive cell proliferation. Cell cycle evolution in the fungal ancestor proceeded through a hybrid network containing both SBF and its ancestral animal counterpart E2F, which is still maintained in early-diverging Fungi such as *Spizellomyces punctatus* (a Chytrid). Chytrids are unique in that they exhibit both fungal and animal-like features, including zoospores that swim using a posterior flagellum nucleated from centrioles, or crawl on surfaces using amoeboid movement.

To address the question of redundancy and specificity of E2F and SBF, we measured the binding specificity of E2F and SBF from several early-diverging Fungi using a protein-binding

microarray (PBM) assay. PBM assays measure, in a single experiment, the binding of recombinant proteins to tens of thousands of synthetic DNA sequences, guaranteed to cover all possible 10-bp DNA sequences in a maximally compact representation. We showed that E2F and SBF from early-diverging Fungi have nearly identical DNA-binding specificity to their human and yeast counterparts. We further showed that E2F and SBF can bind a common set of motifs, which supports the hijacking hypothesis and binding redundancy between E2F and ancestral SBF. Last, we showed that there are specific motifs that can be bound only by E2F or only by SBF. This suggests that certain classes of genes could be under E2F-only or SBF-only control, which may explain why both transcription factors are still maintained in some species, such as *Spizellomyces punctatus*.

09:30 [Coffee Break](#)

Thursday Morning Coffee Break

SPEAKER: [Coffee Break](#)

10:00 [Frank Doyle](#)

Controlling Time in Biology

SPEAKER: [Frank Doyle](#)

ABSTRACT. Maintaining robust circadian rhythms has been linked to longevity and metabolic health. Because these rhythms are disturbed by factors such as jet lag, shift work, and high-fat diets, there is interest in developing pharmacological control strategies to modulate circadian function. The design of therapeutic strategies is currently limited by the lack of a clear mechanistic understanding of interactions between posttranslational regulators, as efficient control of clock behavior will likely require several simultaneous modulations. Although small molecules that modulate clock function might offer therapeutic approaches to such diseases, only a few compounds have been identified that selectively target core clock proteins. Using mathematical modeling and systems biology approaches, we provide a mechanistic interpretation for the relationship between candidate regulators, lending insight into circadian regulation and potential pharmacological control. This study provides further insight into the molecular clock machinery responsible for maintaining robust circadian rhythms.

10:30-12:30 Session 17A: Parallel Session V a:
Emerging Technologies

CHAIR: Xueyang Feng

LOCATION: Brush Mountain A & B

10:30 Nurhezreen Iqbal, Ai Muto, Nozomu Yachie,
Barry Wanner and Hirotada Mori

**Global Outlook on Survival of Escherichia coli
Mutants during Long-Term Stationary Phase**

SPEAKER: Nurhezreen Iqbal

ABSTRACT. In natural environment bacteria seldom encounter optimal conditions that could sustain its growth exponentially. Thus, bacteria have adapted distinctive strategies to survive during famine period; for example, most species of gram-positive bacteria will form dormant spores in response to starvation. Gram-negative bacteria are able to survive this period without entering dormancy. Also, it was shown that *Escherichia coli* can survive for long periods of time (months or even years) under starvation condition and this phase has been termed as long-term stationary phase (LTSP) (Finkel S. E., 2006; PMID 16415927). Two interesting phenomena associated with LTSP; growth advantage in the stationary phase (GASP) and viable but nonculturable (VBNC) phenotypes were observed in cells survival during the stationary phase. GASP phenotype has been characterized as mutant cells that exhibit fitness advantage against wild-type and eventually dominates the culture, which was proven through competition experiments between aged cells and young cells populations. To date, mutations in *rpoS*, *lrp*, *gltIJKL* and subsequently *sgaABC* genes were characterized with GASP phenotype. In addition, VBNC phenotype are seen in many bacteria as a response to a variety of stress though the molecular mechanism of VBNC phenotype have not been cleared. We are interested to study this phenomenon from a systems perspective to understand the function that allows gram-negative bacteria to survive prolonged periods of starvation. For this purpose, we have constructed a new *E. coli* single-gene deletion library, with 20 nucleotides molecular barcode which allows us to monitor population dynamics in mixed culture by high-throughput sequencing. We had grown the mutant library in Luria-Bertani (LB) medium and sampled for three weeks (LTSP) under batch culture condition to monitor population changes of each deletion strains. Serial passage was carried out at each sampling to differentiate between the viable and the non-viable populations.

10:50 [Christian Lieven](#), [Krist Gernaey](#), [Markus Herrgård](#)
and [Nikolaus Sonnenschein](#)

Modeling Methanotrophy: A genome-scale metabolic model of *Methylococcus capsulatus*

SPEAKER: [Christian Lieven](#)

ABSTRACT. Genome-scale metabolic models allow researchers to investigate the metabolism of a given organism in various growth conditions. In addition, they provide a means to calculate yields, to predict consumption and production rates, and to study the effect of genetic modifications, without running resource-intensive experiments. While metabolic models have become an invaluable tool for optimizing industrial production hosts like *E. coli* and *S. cerevisiae*, few such models exist for C1 metabolizers. Here we present a genome-scale metabolic model for *Methylococcus capsulatus*, a well-studied obligate methanotroph, which, since the 70s has been the industry's focus as a production strain of single cell protein (SCP). The model was manually curated, and spans a total of 783 metabolites connected via 840 reactions. The inclusion of 730 genes and a host of annotations, make this model not only a useful tool for knock-out studies, but also a centralized knowledge base for *M. capsulatus*. We are confident that our contribution will serve the ongoing fundamental research of C1 metabolism, and pave the way for rational strain design strategies towards improved SCP production in *M. capsulatus*.

Paper in preparation

11:10 [Adriana San Miguel](#)

High-throughput platforms for deep phenotyping

SPEAKER: [Adriana San Miguel](#)

ABSTRACT. A major challenge in biology is fully understanding the relationship between genotype and phenotype. Decades after genome sequencing emerged, we are far from comprehensive models that can predict phenotypic outcomes from environmental conditions and genetic perturbations. While genomic, proteomic, and metabolomics technologies have greatly advanced in the past decade, phenotyping has not reached the same level of refinement. In this work, we develop tools to extract quantitative phenotypes at multiple levels. We use the multicellular organism *C. elegans* to characterize *in vivo* intermediate and

downstream phenotypic states such as gene expression, cellular and subcellular morphology, and behavior. By incorporating experimental platforms that enable high-throughput imaging, controlled environmental conditions, and on-line image analysis, we are able to extract quantitative phenotypic data sets that enable identifying underlying biological functions and genetic relationships via statistical and mathematical analysis tools. This is made possible by the integration of customized microfluidic platforms and computer vision which allow fast animal handling, controlled environmental conditions, and quantitative image analysis. We have used these tools to identify alleles that produce subtle phenotypes in synaptic patterning. Through statistical analyses, we characterized a spectrum of phenotypic severity exhibited by a library of mutants, rather than a binary outcome. Through mathematical models, genetic relationships can be predicted from phenotypes that are hidden to human vision. In addition, we have developed microfluidic platforms that allow longitudinal lifelong monitoring of *C. elegans* populations, while performing high-resolution imaging. Through these platforms, lifelong spatiotemporal gene expression patterns can be extracted, and correlated with subcellular, cellular and physiological outcomes. These deep-phenotyping tools allow quantitative characterization of intermediate and downstream outcomes (such as spatiotemporal gene expression, cellular and subcellular phenotypes), and thus enable building predictive models that link phenotype and genotype.

11:30 [Elin Nyman](#), [Markus Karlsson](#), [William Lövfors](#),
[Mikael Forsgren](#), [Rasmus Magnusson](#), [Fredrik Eklund](#), [Peter Lundberg](#), [Mika Gustafsson](#) and [Gunnar Cedersund](#)

From omics to decision-support using hybrid mechanistic and machine-learning models

SPEAKER: [Elin Nyman](#)

ABSTRACT. Radiogenomics, systems medicine, and systems pharmacology are some of the fields that try to do essentially the same thing: merge omics-level data with other available data for a patient to obtain a personalized diagnosis and treatment plan. In this talk, I will present our emerging set of inter-connected technologies that do precisely this, by using a hybrid modelling approach combining mechanistic and machine learning models.

For mechanistic modelling of omics level data, we have developed a set of similar approaches allowing us to scale mechanistic models to the omics level. These approaches are based on the identification of a high-quality core model, which describes the most well-studied players in the network, with a sub-division of the remaining estimation problem so that it can be parallelized in smaller sub-problems. This approach has been applied to both genomics and phosphoproteomics data, and constitute some of the first mechanistic models ever developed for the omics level.

We also combine cell-level data with the whole-body level, using multi-level modelling approaches. The key for the translation to the whole-body level is direct measurements of the input-output profile of each sub-module, allowing us to sub-divide the overall multi-level modelling problem.

The models become patient-specific using nonlinear mixed effects modelling, which is a blended hybrid modelling approach, able to incorporate non-mechanistic covariates. We have used this to identify patient-specific biomarkers for the liver, brain, heart, and whole-body level in a way that outperforms existing clinical technologies.

Finally, the new model-generated biomarkers are combined with all other biomarkers in a sequential hybrid modelling scheme. The combined hybrid model can be used to a) simulate the predicted evolution of mechanistically described variables in e.g. diabetes in response to treatments, diet, or medication, and b) predict the resulting updated risk of contracting a stroke or heart attack.

11:50 [Jens Roessler](#), [Weike Pei](#), [Xi Wang](#), [Thorsten B. Feyerabend](#), [Daniel Postrach](#), [Claudia Quedenau](#), [Wei Chen](#), [Sascha Sauer](#), [Hans-Reimer Rodewald](#) and [Thomas Höfer](#)
Computational framework for endogenous barcoding of hematopoietic stem cells in vivo
SPEAKER: [Jens Roessler](#)

ABSTRACT. Understanding the development of tissues and organs at a single cell level remains a challenge. Here we show that Polylox – an artificial DNA recombination locus based on the loxP-Cre recombination system developed recently by Hans-Reimer Rodewald and colleagues – allows for the endogenous, non-invasive barcoding of single cells. Based on a

Markov model for barcode generation, we find that more than 10^6 different barcodes can be generated. However, individual barcodes have different probabilities of generation (as also noticed for alternative barcoding approaches using CRISPR/Cas9). Our model, calibrated against experimental barcoding data, allows the assignment of barcode generation probabilities and thus the selection of low-probability, informative barcodes for clonal analyses. We have used this mathematical framework to analyze data on the formation of hematopoietic stem cells (HSC) clones during development and on the differentiation of mature cell lineages from HSC during development and adult hematopoiesis. Many HSC realize multipotency in vivo, yet the spreading of barcodes from such cells reveals a fundamental split between myel erythroid and lymphoid lineage development. These findings support the long-held, but currently contested, view of a tree-like hematopoietic structure with few major branches.

12:10 [Yi-Jiun Chen](#), [Weikang Wang](#), [Xiaojun Tian](#),
[Daniel E Lefever](#), [David A Taft](#) and [Jianhua Xing](#)
An efficient procedure to generate plasmid for endogenous CRISPR-based knockin
SPEAKER: [Yi-Jiun Chen](#)

ABSTRACT. The CRISPR-based gene-editing tool has revolutionized molecular cell biology research. It makes efficient genome editing possible, and is fundamentally changing our practice in biological research, synthetic biology, biomedical treatment, and other technology development such as biofuels.

CRISPR-based gene knock-in requires synthesis of DNA constructs containing the knock-in sequence as a template. Some constructs have high G/C content and high sequence complementation, and sometimes include a drug selectable marker and associated LoxP sites with palindromic structure. These properties impose severe challenges to any DNA synthesis approach. Specifically, the widely-used Gibson assembly procedure, which here is designed to assemble four DNA segments into a construct, often leads to misassembly. We developed a procedure that greatly improves the efficiency of making the DNA constructs. Experimental tests on multiple constructs confirmed that our new procedure leads to at least 3-8 folds of increase of the assembly efficiency. More impressively we achieved high assembly efficiency on DNA constructs we failed to make otherwise. The

modularized procedures save time and cost while making multiple constructs, and it may accelerate applications of the CRISPR technique in synthetic and systems biology studies.

10:30-12:30 Session 17B: Parallel Session V b:
Computational Methodology I

CHAIR: [Ursula Kummer](#)

LOCATION: Room 342 in Squires

10:30 [Leonie Amstein](#), [Jennifer Scheidel](#), [Jörg Ackermann](#) and [Ina Koch](#)

**Detection of all possible signaling pathways
in complex networks at steady state using
Manatee invariants**

SPEAKER: [Ina Koch](#)

ABSTRACT. Signaling systems control many pivotal processes in a cell, which need to be strictly regulated. The corresponding signaling networks become big and complex with many cross-talks. The automatic detection of all possible signal transduction pathways from the receptor binding to the cell response would be useful for profound network analysis. Even if signaling pathways, which lead, for example to cell death or apoptosis, will not be repeated by the same cell again, the same signaling pathway may take place in the next generation of cells. Thus, a steady-state behavior can be assumed. Elementary mode (EM) analysis [1], which takes into account steady-state conditions, has not only been applied to model metabolic systems, but also to model signaling networks [2]. There are some specific properties in signaling pathways. For example, feedback loops may lead to EMs that do not capture the entire signal flow. To get the complete signaling pathways, we have to combine the EMs in a special way. We expressed EMs as transition invariants (TIs) in the Petri net formalism [3]. To combine the EMs in a proper way, we define Manatee invariants [4] based on feasible TIs [2]. We determine the cause of the disruptions of signal flows as internal place invariants in the subnetwork of a TI and generate the linear combination of TI to link interrelated processes. In the talk, we explain the concept of Manatee invariants, giving the necessary definitions. For illustration, we introduce a Petri net model of mitophagy processes [5] edited and analyzed using the software tool MonaLisa [6]. We will show that at least one EM did not cover a signaling pathway from the receptor to the cell response, while the corresponding Manatee invariant recovers this pathway. 1. Schuster et al.

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Sackmann et al. (2006) BMC Bioinformatics, 7:482 (2006), doi:10.1186/1471-2105-7-482 3.
Koch, Reisig, Schreiber (Eds.) (2011) Springer, Modeling in Systems Biology: The Petri Net Approach 4. Amstein et al. (2017) in revision 5.
Lass (2016) Bachelor's Thesis, Goethe-University Frankfurt/Main 6. Einloft et al. (2013) Bioinformatics, 29: 1469

10:50 [Janaka Edirisinghe](#), [José Faria](#), [Filipe Liu](#), [Joana Xavier](#), [Samuel Seaver](#), [Pamela Weisenhorn](#), [James Jeffryes](#), [Tian Gu](#), [Qizh Zhang](#), [Isabel Rocha](#) and [Christopher Henry](#)

Automated pathway curation and improving metabolic model reconstruction based on phylogenetic analysis of pathway conservation

SPEAKER: [Janaka Edirisinghe](#)

ABSTRACT. Metabolic models generated by automated reconstruction pipelines are widely used for high-throughput prediction of microbial phenotypes. However, the generation of accurate in-silico phenotype predictions based solely on genomic data continues to be a challenge as metabolic models often require extensive gapfilling in order to produce biomass. As a result, the true physiological profile of an organism can be altered by the addition of non-native biochemical pathways or reactions during the gapfilling process. In this study, we constructed draft genome-scale metabolic models for ~1000 diverse set of reference microbial genomes currently available in GenBank, and we decomposed these models into a set of classical biochemical pathways. We then determine the extent to which each pathway is either consistently present or absent in each region of the phylogenetic tree, and we study the degree of conservation in the specific steps where gaps exist in each pathway across a phylogenetic neighborhood. Based on this analysis, we improved the reliability of our gapfilling algorithms, which in turn, improved the reliability of our models in predicting auxotrophy. This also resulted in improvements to the genome annotations underlying our models. We validated our improved auxotrophy predictions using growth condition data collected for a diverse set of organisms. Our improved gapfilling algorithm will be available for use within the DOE Knowledgebase (KBase) platform (<https://kbase.us>).

11:10 [Tom Thorne](#)

Sequential Monte Carlo learning of Bayesian gene regulatory network models from RNA-seq data

SPEAKER: [Tom Thorne](#)

ABSTRACT. Learning of gene regulatory networks from transcriptomic data is challenging due to the large space of potential gene regulatory interactions to explore, and the relative sparsity of data points. Further challenges are presented by RNA-seq data sets where the data cannot be assumed to follow a multivariate normal distribution, and so many previously applied graphical modelling approaches are no longer valid. Building on previous methods from the literature exploiting Gaussian process regression in a variable selection framework, we present a Sequential Monte Carlo approach to learning gene regulatory network structures. Such methods utilise a population of particles to more thoroughly explore the parameter space, and are easily amenable to parallelisation on multicore CPUs or GPGPU systems to accelerate the inference procedure. Each particle represents a potential network structure, and particles are propagated through a sequence of probability distributions, starting as a sample from the prior distribution on network edges, and finishing as a sample from the posterior distribution of the model. We benchmark the performance of our approach when compared to traditional Markov Chain Monte Carlo approaches using synthetic RNA-seq data with known network structure, and apply the method to real world RNA-seq data.

11:30 [Shangying Wang](#), [Kai Fan](#), [Nan Luo](#), [Yangxiaolu Cao](#), [Carolyn Zhang](#) and [Lingchong You](#)

Emulating mechanism-based models with artificial neural networks for applications in synthetic biology and systems biology

SPEAKER: [Shangying Wang](#)

ABSTRACT. Mechanism-based mathematical models are the foundation for diverse applications in science and engineering. It is often critical to explore the massive parametric space for each model. For certain models, e.g., agent-based, PDEs, and SDEs, this practice can impose a prohibitive barrier for practical applications even when computer clusters are used. To overcome this limitation, we develop a fundamentally new framework to improve the computational efficiency by orders of magnitude. The key concept is to train an artificial neural network (ANN) using a limited number of simulations

generated by well-defined mechanism-based models. The number of simulations is small enough such that the simulations are still manageable, but large enough to train the ANN sufficiently well to make reliable predictions. Then, the trained ANN will be used to explore the system dynamics in a much larger parametric space. In addition to the framework, we also illustrate the application of this approach using several hand-on examples in synthetic biology design and in exploring stochastic dynamics of complex networks. Our work can potentially be a platform for faster pattern screening, cell strain identification as well as new drug development.

11:50 [Martin Golebiewski](#), [Steffen Brinkmann](#), [Olga Krebs](#), [Hadas Leonov](#), [Quyen Nguyen](#), [Stuart Owen](#), [Natalie Stanford](#), [Andreas Weidemann](#), [Ulrike Wittig](#), [Katy Wolstencroft](#), [Jacky L. Snoep](#), [Wolfgang Müller](#) and [Carole Goble](#)

Data Needs Structure: Data and Model Management for Distributed Systems Biology Projects

SPEAKER: [Martin Golebiewski](#)

ABSTRACT. We develop and offer integrated data management support for research in the fields of systems biology and systems medicine within and across research consortia. This support is applied and offered to geographically dispersed, interdisciplinary and large-scale research initiatives in which we are part of, like the German systems biology network Virtual Liver and its successor the research initiative ‘Systems Medicine of the Liver’ (LiSyM: <http://www.lisym.org>), as well as European research networks like ERASysAPP, the former SysMO network (Systems Biology of Microorganisms) or NMTrypl (New Medicines for Trypanosomatidic Infections). Parts of these solutions are also applied to projects with a local focus as the Synthetic Biology Centres at Manchester (SynBioChem) and Edinburgh (SynthSys).

Our data management concept aims at bundling, storing and integrating research assets like data, models and description of processes and biological samples in a Findable, Accessible, Interoperable and Reusable (FAIR) manner (<http://fair-dom.org>) and consists of 4 major pillars:

- 1) Infrastructure backbone: The SEEK software as registry and a commons for data, models, samples, processes and resulting publications or

presentations, at the same time yellow pages for projects, people and events. SEEK is either implemented as data management platform that is maintained by the research project itself (e.g. LiSyM SEEK: <http://seek.lisym.org>) or as hub service maintained by us and spanning different consortia (FAIRDOMhub: <https://www.fairdomhub.org>).

- 2) Standardized data description: Data spreadsheet templates and tailored use of controlled vocabularies and ontologies to describe data and metadata.
- 3) Modelling support: Seamless handling and simulation of models by integrated modelling platforms (JWS-Online, SYCAMORE, Cytoscape).
- 4) Social support: Facilitators (PALs) in the projects for gathering requirements and dissemination

Unlike the majority of data management systems, we specifically support the interaction between modelling and experimentation. Datasets can be associated with models and/or workflows or biological samples, and model simulations can be compared with experimental data.

12:10 [Jose Cadena](#), [Andrew Warren](#), [Rebecca Wattam](#),
[Allan Dickerman](#) and [Anil Vullikanti](#)

Finding coordinated expression motifs in RNA-seq data

SPEAKER: unknown

ABSTRACT. Advances in high-throughput sequencing technologies have led to a high volume of public RNA-seq data, enabling assembly of large data sets to search for novel biological patterns not visible to individual studies, although methods for doing so remain a significant challenge.

The use of clusters and bi-clusters is a popular unsupervised machine learning approach for discovering co-expressed, and hence functionally related, gene sets. Different notions of clustering have been used, including graph-theoretical methods based on density and hierarchical clustering. Expression data can be viewed as a signed dataset, with up or down regulation captured by a positive or negative quantity, respectively. However, most of these prior approaches tend to ignore the signs and works on unsigned data. This is partly because the

analysis of signed data tends to be much more challenging.

We develop a novel approach for finding coordinated motifs of expression by formalizing them as quasicliques in signed networks. This is computationally much harder than the problem in unsigned networks, and we use a convex optimization approach, combined with pruning, to find the top k quasicliques, in terms of their objective values. We incorporate functional similarity measures on nodes in quasicliques, e.g., the fraction of genes within each cluster that have high scores of semantic similarity as annotated on the Gene Ontology. Clusters with low known functional similarity can be indicators of new biological patterns in such data, and might help guide further experiments. We also study a new approach that involves finding quasicliques with given constraints on the level of functional similarity within the nodes. We evaluate these methods and present findings from analysis of a large compilation of RNA-seq expression data from humans.

10:30-12:30 Session 17C: Parallel Session V c: Cell Decision Making II

CHAIR: [Sylvia Plevritis](#)

LOCATION: Old Dominion Ballroom

10:30 [Jignesh Parmar](#) and [Pedro Mendes](#)

A mathematical model of iron dynamics in a mouse

SPEAKER: [Jignesh Parmar](#)

ABSTRACT. We developed a computational model of mouse iron physiology to gain insights into its complex hormonal regulations. Model calibration revealed an essential role of non-transferrin bound iron (NTBI) uptake by the liver under high iron diet condition, without this the model failed to explain iron distribution in the liver and red blood cells . The model was validated by its ability to simulate the pathophysiology of several iron disorders such as hemochromatosis, β-thalassemia and anemia of inflammation. We also tested various other experimental observations under normal and pathological states which not only further validated our model but also provided better understanding of underlying mechanisms. Moreover, we show that how such a model can be used for optimal therapies of various iron disorders. This physiological model paves the way for a more comprehensive multiscale model across organs, cells, and molecules and also provides a

prototype for human iron metabolism. The present model contributes to a deeper understanding of iron physiology and can be used for predictive exploration of therapeutic interventions in iron disorders.

10:50 [James Lee](#), [Pei-Yin Shih](#), [Oren Schaedel](#), [Porfirio Quintero-Cadena](#), [Alicia Rogers](#) and [Paul Sternberg](#)

Stress-adaptive decision-making and dispersal behaviors in nematodes involve coordinated neuropeptide signaling

SPEAKER: [James Lee](#)

ABSTRACT. Animals, including humans, can cope with environmental stress by adapting their physiology and behavior. The free-living nematode *Caenorhabditis elegans* can adapt to harsh environments by undergoing a whole-animal change, which involves exiting reproductive development and entering the stress-resistant dauer larval stage. The dauer is a dispersal stage with dauer-specific behaviors that allow *C. elegans* to find and stow onto carrier animals for transportation to improved environments, but how the dauer acquires these behaviors, despite having a physically limited nervous system of 302 neurons, is poorly understood. We compared dauer and reproductive development using whole-animal RNA-seq at fine time points, and at sufficient depth to measure transcriptional changes within single cells. We detected 8,042 differentially expressed genes (39% of the protein-coding genome) during dauer and reproductive development, and observed striking up-regulation of 60 of the 118 *C. elegans* neuropeptide genes during dauer entry. We knocked down a large set of neuropeptides using sbt-1 mutants, which are defective in neuropeptide processing, and demonstrated that neuropeptide signaling promotes the dauer entry decision over reproductive development. We then demonstrated that neuropeptide signaling in dauers promotes the dauer-specific nictation (a carrier animal-hitchhiking) behavior, and is necessary for switching from CO₂ (a carrier animal cue) repulsion in non-dauers to CO₂ attraction in dauers. We then tested individual neuropeptides using CRISPR knockouts and existing strains, and revealed that the combined effects of two neuropeptide genes, flp-10 and flp-17, strongly explain the sbt-1 effects on nictation and CO₂ attraction. Through a meta-analysis, we discovered a shared up-regulation of neuropeptides in dauers and the dauer-like

infective juveniles of diverse parasitic nematodes, suggesting the anti-parasitic potential of targeting SBT-1 in these species. Our findings reveal that *C. elegans* animals can adapt to stress by using neuropeptides to enhance their decision-making accuracy, and to expand their behavioral repertoire.

11:10 [Akram Mohammed, Bhanwar Lal Puniya](#) and
[Tomas Helikar](#)

A comprehensive dynamical network model of the human immune system

SPEAKER: [Akram Mohammed](#)

ABSTRACT. The human immune system is well characterized for its critical role in host defense. It has evolved into a complex defense network that recognizes and protect against a range of pathogens that threaten the host viability. Computational models of immune system dynamics may contribute to a better understanding of the relationship between complex phenomena and immune response with respect to various pathogens. While computational models have been developed to study the dynamics of individual functions of the immune system (e.g., immune-receptor signaling, immune response to a tumor antigen, HIV infection of macrophage cells, etc.), recent efforts lack comprehensive computational models capable of capturing the multi-cellular, system-wide complexity of the immune system. We developed a multi-cellular computational network model that integrates various components of the immune system. Specifically, the model includes immune cells (antigen-presenting cells, monocytes, erythrocytes, lymphocytes, granulocytes etc.), non-immune cells (epithelial cells, endothelial cells, keratinocytes, hepatocytes, etc.), cytokines, chemokines, and pathogens (Influenza A virus, Human immunodeficiency virus, Human papillomavirus, Ebolavirus, *Mycobacterium tuberculosis*, *Plasmodium falciparum*, *Leishmania donovani*, *Ascaris lumbricoides*, *Candida albicans*). The network model was manually curated and annotated and consists of 152 components and 456 interactions, which enable the understanding of how the different complex phenomena interact with structures and elements during an immune response. The comprehensive nature of the model simulated a mounted response to nine different pathogens (and/or any combination thereof). Analyses of the dynamical model under a range of simulated conditions validated the

existing immune responses and revealed complex signatures of the immune system during single infection and co-infections. The intuitive model construction allowed us to make novel predictions and validations to gain insights into different infectious diseases. The computational model would be very useful for the biomedical community to generate new hypotheses through iterative interactions with the model and its simulations.

11:30 [Michael Hopkins](#), [John Tyson](#) and [Bela Novak](#)
A common role for stoichiometric inhibitors in cell cycle transitions
SPEAKER: [John Tyson](#)

ABSTRACT. The cell division cycle is the process by which eukaryotic cells replicate their chromosomes and partition the sister chromatids to two daughter cells. To maintain the integrity of the genome, proliferating cells must be able to block progression through the division cycle at key transition points (called ‘checkpoints’), if there have been problems in the replication of the chromosomes or their biorientation on the mitotic spindle. These checkpoints are governed by protein-interaction networks, composed of phase-specific cell-cycle activators and inhibitors. Examples include: Cdk1:Clb5 and its inhibitor Sic1 at the G1/S checkpoint in budding yeast, APC:Cdc20 and its inhibitor MCC at the metaphase checkpoint, and PP2A:B55 and its inhibitor ENSA at the mitotic-exit checkpoint. Each of these inhibitors (I) is a substrate as well as a stoichiometric inhibitor of the cell-cycle activator (A). Because the production (or actuation) of each inhibitor is promoted by a regulatory protein (R) that is itself inhibited by the cell cycle activator, the A-I-R interaction network presents a regulatory motif characteristic of a ‘feedback-amplified domineering substrate’. In this short talk/poster, we describe how the FADS motif responds to signals in the fashion of a bistable toggle switch, and then we discuss in detail how this toggle switch accounts for the abrupt and irreversible nature of three specific cell-cycle checkpoints: at the G1/S transition, at metaphase, and at mitotic exit.

11:50 [Udaya Sree Datla](#), [William H. Mather](#), [Sheng Chen](#), [Isaac W. Shoultz](#), [Uwe C. Tauber](#), [Caroline N. Jones](#) and [Nicholas C. Butzin](#)
The spatiotemporal network dynamics of acquired resistance in an engineered microecology

SPEAKER: [Udaya Sree Datla](#)

ABSTRACT. Great strides have been made in the understanding of complex networks; however, our understanding of natural microecologies is limited. Modeling of complex natural ecological systems has allowed for new findings, but these models typically ignore the constant evolution of species. Due to the complexity of natural systems, unanticipated interactions may lead to erroneous conclusions concerning the role of specific molecular components. Modeling of synthetic microecologies has allowed researchers to explore specific questions (e.g. evolution and maintenance of coexistence) using simplified models, the findings of which can be used to infer results about natural systems. Using synthetic systems, researchers have been able to engineer better-defined cellular interactions and thus shed light on how these interactions lead to particular collective cell behaviors. Most of the microbial association studies involve co-cultures and fail to reflect the spatial relationship which is important to study pattern formation and evolution. The first synthetic predator-prey ecosystem showed the oscillatory population dynamics arising from the interaction of quorum-sensing modules in a spatiotemporal fashion. Recently, a large step forward in the field was the analysis of the microbial evolution and growth arena (MEGA)-plate where the spatiotemporal dynamics of microbial evolution of a single type of motile *Escherichia coli* was studied on an antibiotic background. We use a synthetic system to understand the spatiotemporal dynamics of growth and to study acquired resistance *in vivo*. Our system differs from previous systems in that it focuses on the evolution of a microecology from a killer-prey relationship to coexistence using two different non-motile *E. coli* strains. Using empirical data, we developed the first ecological model emphasizing the concept of the constant evolution of species, where the survival of the prey species is dependent on location (distance from the killer) or on the evolution of resistance. Our simple model, when expanded to complex microecological association studies under varied spatial and nutrient backgrounds may help to understand the complex associations between multiple species in intricate natural ecological networks.

12:10 [Xi-Ming Sun, Anthony Bowman, Samuel Marguerat and Vahid Shahrezaei](#)
Global regulation of transcription by cell size
SPEAKER: [Anthony Bowman](#)

ABSTRACT. Transcriptional output scales genome-wide with cell-size and growth rates. As a result, cells of different size and physiological states contain different numbers of mRNAs and proteins. The molecular mechanisms underlying this remarkably coordinated regulation remain largely mysterious. We have used single molecule FISH (smFISH) to investigate the role of cell size in regulation of transcription at the single cell level. Using fission yeast size mutants, we find that mRNA numbers of a series of diagnostic genes increase proportionally with cell size. Interestingly, we observe that scaling of mRNA numbers with cell size is linear across size mutants and as single cells progress through the cell cycle. We use mathematical models of stochastic gene expression in growing and dividing cells and Bayesian statistical inference to shed light on the source of this linear relationship between transcription and cell size. Our models suggest that for mRNAs with lifetimes shorter than a cell cycle duration, linear scaling is evidence for direct coordination of parameters of gene expression such as transcription or mRNA degradation with cell size. Moreover, we find that noise in mRNA numbers is mainly explained by the cell cycle and random birth-deaths of mRNA molecules with no evidence of transcriptional bursting occurring in constitutively expressed genes. This indicates that either transcription rate or mRNA lifetime, but not the frequency of promoter activation, are scaling with cell size. Using smFISH to quantify nascent mRNA we provide direct evidence of transcription rate being cell size dependent. Finally, we use the power of yeast genetics to explore further the mechanistic origin of the global coupling of gene expression and cell size.

12:30-14:00 Session : Thursday Lunch

LOCATION: Commonwealth Ballroom

14:00-16:30 Session 18: Thursday Afternoon

CHAIR: [John Tyson](#)

LOCATION: Colonial Hall

14:00 [Bela Novak](#)

Keynote Talk: Cell cycle regulation by systems-level feedback controls

SPEAKER: [Bela Novak](#)

ABSTRACT. In order to maintain genome integrity and an effective nucleocytoplasmic ratio from one generation to the next, cells carefully monitor progression through their replication-division

cycle and fix any errors before they jeopardize the progeny of the cellular reproduction process. These error surveillance and correction mechanisms operate at distinct ‘checkpoints’ in the cell division cycle, where a growing cell must ‘decide’ whether it must wait for errors to be corrected or it may proceed to the next phase of the cell cycle. Once a decision is made to proceed, the cell unequivocally enters into a qualitatively different biochemical state, which makes cell cycle transitions switch-like and irreversible. These characteristics of cell cycle transitions are best explained by bistable switches with different activation and inactivation thresholds, resulting in a hysteresis effect. Almost 25 years ago, John Tyson and I proposed that the activity of the mitosis-inducing protein kinase, Cdk1:CycB, is controlled by an underlying bistable switch generated by positive feedbacks involving inhibitory phosphorylations of the kinase subunit. Numerous predictions of this model were experimentally verified by different groups, and bistability has become a paradigm of cell cycle transitions. The phosphorylation of mitotic proteins by Cdk1:CycB is counteracted by a protein phosphatase, PP2A:B55, which is inhibited during mitosis by a stoichiometric binding partner, ENSA-P, which is itself activated by Greatwall-kinase. Using mathematical modelling guided by biochemical reconstitution experiments, we showed recently that the BEG (B55-ENSA-Greatwall) pathway also represents a bistable, hysteretic switch controlled by the activity of Cdk1:CycB. Bistable regulation of the kinase (Cdk1:CycB) and the phosphatase (PP2A:B55) makes hysteresis a robust property of mitotic control, with suppression of futile cycling of protein phosphorylation and dephosphorylation during M phase. These considerations show that both entry into and exit from mitosis are controlled by bistable switches intimately connected to the activities of the major mitotic kinase, Cdk1:CycB, and phosphatase, PP2A:B55. Intriguingly, the ‘design principle’ of the BEG pathway is operative as well at two other cell cycle checkpoints, as will be discussed.

15:00 [Hiroki R. Ueda](#)

Systems Biology of Mammalian Sleep/wake Cycles

SPEAKER: [Hiroki R. Ueda](#)

ABSTRACT. The detailed molecular mechanisms underlying the regulation of sleep duration in mammals are still elusive. To address this challenge, we constructed a simple computational

model, which recapitulates the electrophysiological characteristics of the slow-wave sleep and awake states. Comprehensive bifurcation analysis predicted that a Ca²⁺-dependent hyperpolarization pathway may play a role in slow-wave sleep and hence in the regulation of sleep duration. To experimentally validate the prediction, we generate and analyze 26 KO mice. Here we found that impaired Ca²⁺-dependent K⁺ channels (Kcnn2 and Kcnn3), voltage-gated Ca²⁺ channels (Cacna1g and Cacna1h), or Ca²⁺/calmodulin-dependent kinases (Camk2a and Camk2b) decrease sleep duration, while impaired plasma membrane Ca²⁺ ATPase (Atp2b3) increases sleep duration. Genetical (Nr3a) and pharmacological intervention (PCP, MK-801) and whole-brain imaging validated that impaired NMDA receptors reduce sleep duration and directly increase the excitability of cells. Based on these results, we propose a hypothesis that a Ca²⁺-dependent hyperpolarization pathway underlies the regulation of sleep duration in mammals.

15:30 [Coffee Break](#)

Thursday afternoon Coffee Break

SPEAKER: [Coffee Break](#)

16:00 [Leslie Loew](#)

Multiphysics models of actin regulation

SPEAKER: [Leslie Loew](#)

ABSTRACT. Actin is the most abundant protein in eukaryotic cells and is responsible for their dynamic structures. It accomplishes its function through interaction with a multitude of binding partners and signaling proteins, which control the assembly and branching of actin polymers. Thus signaling, polymerization and mechanics all play important roles in actin function. But accounting for this complex interplay of physics and chemistry presents modeling challenges that require multiple approaches. I will illustrate several such approaches with models and experiments aimed at elucidating actin dynamics in: motile dendritic filopodia, invasive pathogen motility and the leading lamelipodium of a migrating cell,. All these are deterministic models require the solution of partial differential equations in 1, 2, and 3 dimensions respectively. I will also introduce results on upstream signaling to the actin cytoskeleton within the foot processes of kidney podocytes in which the multivalent interactions between nephrin, Nck and NWAsp can produce multivalent clusters. This last system is modeled with stochastic Langevin dynamics

simulations. (Supported through NIH Grant Number P41 GM103313 from the National Institute for General Medical Sciences.)

16:30-18:30 Session 19A: Parallel Session VI a:
Regulatory Network I

CHAIR: [Jake Tu](#)

LOCATION: Brush Mountain A & B

16:30 [Scott Rata](#), [Stephy Joseph](#), [Helfrid Hochegger](#)
and [Bela Novak](#)

**Two interlinked bistable mechanisms
generate a robust M phase**

SPEAKER: [Scott Rata](#)

ABSTRACT. In order to maintain chromosome number between mitotic cell cycles, it is essential that the transition from interphase to M phase is abrupt and irreversible. This transition requires the switch-like phosphorylation of hundreds of proteins by the cyclin-dependent kinase 1 (Cdk1):cyclin B (CycB) complex. Previous studies have ascribed these switch-like phosphorylations to the self-activation of Cdk1:CycB through the removal of inhibitory phosphorylations on Cdk1-Tyr15, which creates a bistable switch that makes mitotic commitment irreversible.

Cdk1 self-activation, however, is dispensable for irreversible, switch-like mitotic entry due to a second mechanism that has recently been discovered: Cdk1:CycB inhibits one of its major counteracting phosphatases (PP2A:B55) via Greatwall kinase, which is phosphorylated and activated by Cdk1:CycB and then inhibits PP2A:B55 by phosphorylating the small, heat-stable protein ENSA. PP2A:B55 in turn dephosphorylates and inactivates Greatwall, forming a double negative feedback loop that gives a bistable PP2A:B55 activity profile with respect to Cdk1:CycB activity (1). PP2A:B55 also dephosphorylates Wee1 and Cdc25, generating crosstalk between the two modules. The resulting network that we are investigating – of two bistable mechanisms that mutually inhibit each other, is one that operates with maximum theoretical switching efficiency and is therefore ideal for the transitions between interphase and M phase.

Based on this theoretical framework we have explored these bistable mechanisms and their crosstalk combining experiments in HeLa cells with mathematical modelling. Our data suggest that two interlinked bistable mechanisms provide a robust solution for irreversible and switch-like mitotic entry and that either mechanism can

maintain a bistable system response. When either of the bistable mechanisms are removed experimentally, hysteresis is maintained but reduced; when they are both removed, hysteresis is lost. In summary, we show how two mutually inhibiting bistable mechanisms generate robust separation of interphase and M phase.

Reference: 1. Mochida et al. (2016): Curr. Biol. 26: 3361–3367

16:50 [Christoph Kommer](#), [Qin Zhang](#), [Ahmed Hegazy](#), [Max Löhning](#) and [Thomas Höfer](#)

A data-driven correlation measure model for epigenetic network inference in T cells

SPEAKER: [Christoph Kommer](#)

ABSTRACT. CD4+ T-helper cells direct the cell-based and antibody-based arms of the adaptive immune system via the secretion of cytokines. The classical view has been that naïve T-helper (Th) cells differentiate into a small number of distinct stable states that express certain cytokine profiles (Th1, Th2 etc.). Recently this view has been challenged by experimental findings that suggest a higher complexity and point towards a long-lived tunable continuum of cell states between the well-known extremes. These hybrid states stably co-express graded levels of lineage-specifying transcription factors, such as T-bet and GATA-3. The mechanistic basis of such a stable continuum of cell states is unknown. To interrogate the underlying gene-regulatory mechanisms, we integrated data on histone modification patterns, RNA expression and transcription factor binding to systematically identify enhancers and repressors involved in Th cell lineage specification, map these regulatory elements to their target genes and identify their control by transcription factors, thus obtaining a bipartite graph linking enhancers and genes. To this end, we developed a novel correlation model, via a data-driven multivariable histone correlation measure, for inferring enhancer/repressor-gene interactions on topologically associated domains. This approach recovered well-known cis-regulatory elements and predicted new ones with comparable statistical confidence. We then used machine learning approaches to classify the large number of individual enhancers into functional classes according to their regulation by the lineage-specifying transcription factors T-bet and GATA-3 as well as external differentiation signals. This comprehensive topological analysis provides the basis for understanding the multistable dynamics of the Th cell differentiation network.

17:10 [Federico Reali](#), [Melissa Morine](#), [Ozan Kahramanoğulları](#), [Suryaprakash Raichur](#), [Hans-Christoph Schneider](#), [Daniel Crowther](#) and [Corrado Priami](#)

Mechanistic interplay between ceramide and insulin resistance

SPEAKER: [Federico Reali](#)

ABSTRACT. A growing number of studies have elucidated the essential role of ceramides and sphingolipids in the glucose homeostasis and insulin signaling. However, the mechanistic interplay between various components of ceramide metabolism remains to be quantified. To this end, we have resorted to dynamical modeling to gain insights into the sphingolipid metabolism and their role in the development of the insulin resistance. In particular, we have focused on the C16 ceramides family. Our model extends and refines a previously published model by including those reactions that connect sphingolipids de-novo synthesis with the salvage pathway. The latter recycles complex sphingolipids by transforming them in ceramides and it accounts for a significant part of the total ceramide production. We estimated unknown parameters of the model using mice macrophage cell line data. For the parameter estimation, we have used a multi-start approach with a least squares method. We have validated this extended model on an independent dataset for the same tissue in mice. We have integrated the model with transcriptomic data from a different experiment in obese/diabetic murine macrophages at 5 and 16 weeks. Our *in silico* experiments on the behavior of ceramide and related bioactive lipids, in accordance with the observed transcriptomic changes, support the observation on insulin resistance at the later phase. Furthermore, it provides a mechanistic explanation of its development. Our model suggests the key role of ceramide, glucosylceramide, and S1P in the development of insulin resistance. In addition, sensitivity analysis on the model allowed us to quantify the effect of the availability of each enzyme involved in the metabolism on each sphingolipid. We have visualized such effects using an interaction network. These visualizations should guide wet lab scientist in identifying new potential drug targets. In addition, the visualizations may help in identifying collateral effects by highlighting the nontrivial interactions among all the metabolites, supporting the development of more precise drugs. This article is published in January 2017, at the Nature Publishing Group journal of

17:30 [Thierry Mondeel](#), [Christian Linke](#), [Silvia Tognetti](#),
[Rainis Venta](#), [Mart Loog](#), [Hans Westerhoff](#),
[Francesc Posas](#) and [Matteo Barberis](#)

THE MULTIPLEX PHASE INTERLOCKER – A NOVEL AND ROBUST MOLECULAR DESIGN SYNCHRONIZING TRANSCRIPTIONAL CELL CYCLE DYNAMICS

SPEAKER: [Matteo Barberis](#)

ABSTRACT. The eukaryotic cell cycle is robustly designed, with molecules interacting and organized within definite network topologies that ensure its precise timing. This is governed by a transcriptional oscillator interlocked with waves of dedicated enzymatic activities, called cyclin-dependent kinases (cyclin/Cdk). These guarantee execution of definite phases throughout cell cycle progression. Although details about transcription of cyclins, the regulatory subunits of these enzymes, are available, a lack of understanding exists about network motifs responsible for the precise timing of waves of cyclin activation. We investigate the robustness of molecular designs interlocking the transcriptional oscillator with waves of cyclin/Cdk1 kinase activities. We have recently identified a transcriptional cascade that regulates the relative timing of waves of mitotic (Clb) cyclin expression in budding yeast. This cascade involves the Forkhead (Fkh) transcription factors (TF). Here we aim to unravel the network motif(s) responsible for timely cyclin/Cdk1 dynamics that interlock Clb waves through Fkh-mediated signaling. An integrated computational and experimental framework is presented. A kinetic model of the cyclin/Cdk1 network is simulated under a quasi-steady state assumption, and fitted to *in vivo* time course data of Clb dynamics. Robustness analyses are then performed by testing 1024 possible network motifs for their ability to fit Clb oscillations. Biochemical experiments support computational analyses, revealing the Clb/Cdk1-Fkh2 axis to be pivotal for timely transcriptional dynamics. A novel regulatory motif synchronizing Clb waves, coined as Multiplex Phase Interlocker, is unraveled. This motif uniquely describes a molecular timer (TF) that relies on separate inputs (cyclin/Cdk1 complexes) converging on a common target (TF itself). Within the motif, a progressive TF (Fkh2) activation may be realized by the sequential Clb/Cdk1 complexes. Altogether, our integrative approach is able to pinpoint robustness of cell cycle control by revealing a novel and conserved principle of design that ensures timely oscillations

of cyclin/Cdk1 activities.

17:50 [Emily Miraldi](#), [Maria Pokrovskii](#), [Jason A. Hall](#),
[Dayanne Martins de Castro](#), [Ren Yi](#), [Nick De
Veaux](#), [Nicholas Carriero](#), [Aaron Watters](#), [Dan R.
Littman](#) and [Richard Bonneau](#)

**Transcriptional regulatory network inference
from gene expression and chromatin
accessibility measurements**

SPEAKER: [Emily Miraldi](#)

ABSTRACT. The Assay for Transposase Accessible Chromatin (ATAC)-seq provides a unique opportunity for inference of the transcriptional regulatory networks (TRN), especially for cell types and contexts where sample material is limiting and a priori knowledge of transcriptional regulation is scarce. Integration of accessible chromatin regions with TF motif database provides an initial network, where putative interactions are based on TF motif occurrences *cis* to gene loci. This initial network contributes to network inference in two ways (1) as a network prior for downstream inference and (2) to estimate TF activities (TFAs) from putative target gene expression levels (as opposed to more traditional estimates based on TF mRNA levels). The TFAs, network prior, and target gene expression then serve as input to the Inferelator algorithm, which uses Bayesian best subset regression to learn the entire transcriptional regulatory network. Noisy prior network edges that lack support from the gene expression measurements are removed, while new edges can be learned. We first validate our method in T Helper 17 (Th17) cells, integrating new ATAC-seq data with published RNA-seq data and making use of TF knockout and ChIP-seq to evaluate model performance. Then we infer TRNs for the relatively recently discovered innate lymphoid cells (ILCs), where very few transcriptional regulatory interactions are known. We validate the ILC TRN models both computationally (using gene expression prediction in new tissues) and experimentally through TF perturbation response measurements. We rigorously demonstrate the strength of our method to learn predictive transcriptional regulatory network models from ATAC-seq and RNA-seq experimental designs.

18:10 [Neil Adames](#), [Pavel Kraikivski](#), [Aditya Pratapa](#), [T.
M. Murali](#), [John Tyson](#) and [Jean Peccoud](#)

**Using high-throughput genetics to test
mathematical models of the yeast cell cycle**

SPEAKER: [Neil Adames](#)

ABSTRACT. When developing mathematical models of biochemical processes, the relative paucity of quantitative data concerning concentrations of molecular species and especially reaction rates makes parametrization a challenge. On the other hand, experimentalists have obtained large amounts of phenotypic data from mutants in model organisms. Although such data do not provide specific values for model parameters, fitting models to these phenotypes can significantly constrain parameter sets. In the past, we have used existing phenotypic data in the literature to develop models of the yeast cell cycle, and then tested model predictions by generating a few dozen new cell cycle mutants. To address the bottle neck of experimental validation, we have scaled up the generation of new yeast cell cycle mutants using the synthetic genetic array (SGA) approach. Using selectable markers for haploid cells and gene deletions, SGA facilitates large-scale genetic crosses performed in arrays of 96 up to 1536 crosses per plate. Instead of only testing pairwise genetic interactions, we will be making strains with combinations of up to 6 deletion mutations. We are currently in the process of generating a set of ~3000 yeast cell mutants that our current model predicts to be synthetic lethal combinations or to rescue synthetic lethal combinations. The observed genetic interactions will either confirm aspects of the model or allow us to infer new molecular interactions and to further tune our model parameters.

16:30-18:30 Session 19B: Parallel Session VI b:
Computational Methodology II

CHAIR: [Stefan Hoops](#)

LOCATION: Room 342 in Squires

16:30 [Xiao Ma](#), [Onur Dagliyan](#), [Klaus Hahn](#) and
[Gaudenz Danuser](#)

An Adaptive Spatiotemporal Spectrum Decomposition Approach for Cellular Morphodynamic Profiling

SPEAKER: [Xiao Ma](#)

ABSTRACT. Cellular morphology and morphodynamics are commonly used for qualitative and quantitative assessments of cellular states, since they are the phenotypic outcome of cellular processes such as differentiation, proliferation, migration, and apoptosis. Here we propose a framework to profile cellular morphodynamics based on an adaptive spectrum decomposition approach, in

which time series of local cell boundary motion is decomposed and profiled into analytical instantaneous frequency spectra defined by the Hilbert-Huang transform (HHT), with a spatial and temporal resolution that matches the dimension of localized protrusion events. For an isogenic, clonal population of spontaneously protrusive Cos7 fibroblast, we found that the instantaneous frequency distributions are remarkably consistent in spite of vast cell-to-cell heterogeneity in cell boundary motion magnitude. Meanwhile, by acute silencing of the Vav2 GEF which activates Rac1 signaling, we discovered frequency distribution shifts. From this data we conclude that the frequency spectra encode the state of molecular regulation that governs the local cellular morphodynamic behavior, whereas the cell boundary motion magnitude merely captures the activation level of a given regulatory regime.

Next, we adopted the profiled frequency spectra as features to divide the cell periphery into sub-regions with different morphodynamic behavior using a statistical region merging (SRM) algorithm in space and time. To evaluate and verify the clustering accuracy and quality, we then monitored Rac1 activity of Cos7 cells in clustered sub-regions of cell periphery with distinct morphodynamic profiles. The quantification results did identify different levels of local signaling strength and signaling coordination in those sub-regions. We claim that the proposed framework serves as a pre-classifier of cell boundary motion with consistent molecular states, which is of significance to further investigate the spatiotemporal coupling between cellular morphodynamics and underlying molecular regulation.

16:50 [Håvard G. Frøysa](#), [Hans J. Skaug](#) and [Guttorm Alendal](#)

Structural identifiability of kinetic parameters

SPEAKER: [Håvard G. Frøysa](#)

ABSTRACT. Metabolic networks are typically large and contain many metabolites and reactions. This results in dynamical models consisting of large systems of ordinary differential equations having many kinetic parameters. These parameters, however, are often unknown and must be estimated from experimental data. In our work, we assume the data to be metabolomics measurements of various steady states obtained by different input flux configurations to the network. Under the assumption of first order kinetics and normally distributed error terms, we are able to calculate the Fisher information matrix

analytically for the unknown kinetic parameters. This enables us to study the structural identifiability of the kinetic parameters, i.e. if data can provide the information needed for estimation of the parameters or not for given input fluxes. If the input fluxes are controllable, the so-called D-optimality criterion can be used to find the optimal configuration of input fluxes that maximizes the information. In some cases, adding more measurements does not increase the information about the parameters. For smaller test networks this can be shown visually, and we are able to explain and predict the properties of the Fisher information matrix by the use of extreme pathways. Altogether, our work provides a methodology for analyzing the identifiability of kinetic parameters from steady state metabolomics data using various mathematical properties of the Fisher information matrix.

Acknowledgements: This research was supported by the Research Council of Norway through grant 248840.

17:10 [Mansooreh Ahmadian](#), [Shuo Wang](#), [John Tyson](#) and [Young Cao](#)

Hybrid ODE/SSA Model of the Budding Yeast Cell Cycle Control Mechanism with Mutant Case Study

SPEAKER: [Mansooreh Ahmadian](#)

ABSTRACT. The budding yeast cell cycle is regulated by complex and multi-scale control mechanisms, and is subject to inherent noise, resulted from low copy numbers of species such as critical mRNAs. Conventional deterministic models cannot capture this inherent noise. Although stochastic models can generate simulation results to better represent inherent noise, the stochastic approach is often computationally too expensive for complex systems, which exhibit multi-scale features in two aspects: species with different scales of abundances and reactions with different scales of firing frequencies. Moreover, it often requires detailed information of chemical kinetics, which is either not available or costly. To address this challenge, one promising solution is to adopt a hybrid approach. Hybrid stochastic method replaces the single mathematical representation of either discrete-stochastic or continuous deterministic formulation with an integration of both approaches, so that the corresponding advantageous features are well kept to achieve a trade-off between accuracy and efficiency. In this

work, a comprehensive deterministic model is augmented first by adding mRNAs as the source of intrinsic noise in cell cycle. Second, we propose a hybrid stochastic model that represents a gene-protein regulatory network of the budding yeast cell cycle control mechanism, respectively, by Gillespie's stochastic simulation algorithm (SSA) and ordinary differential equations (ODEs). Simulation results of our model are compared with published experimental measurement on the budding yeast cell cycle. The comparison demonstrates that our hybrid model well represents many critical characteristics of the budding yeast cell cycle, and reproduces phenotypes of more than 100 mutant cases. Moreover, the model accounts for partial viability of certain mutant strains. The last but not the least, the proposed scheme is shown to be considerably faster in both modeling and simulation than the equivalent stochastic simulation.

17:30 [Egils Stalidzans](#), [Vitalijs Komasilovs](#) and [Agris Pentjuss](#)

Total enzyme activity constraint and homeostatic constraint impact on the best adjustable parameter sets of a kinetic model

SPEAKER: [Egils Stalidzans](#)

ABSTRACT. Model based design of biochemical networks of microorganisms with improved target metabolite yield or flux is a typical kinetic model optimization task. Selecting efficient small set of adjustable parameters to improve metabolic features of an organism is important to reduce implementation costs and risks of unpredicted side effects. The feasibility of optimization result can be improved by integration of biologically and biochemically relevant constraints during the optimization of kinetic models. Implementation of constraints reduces the impact of suggested changes in processes that are out of the scope of the model. This increases the probability that the result of kinetic model optimization can be carried out by an organism after its introduction *in vivo*. A case study was carried out to determine the impact of total enzyme activity and homeostatic constraints on the objective function values and the following ranking of adjustable parameter combinations. The total enzyme activity constraint limits the overexpression of enzymes by taking into account the limits of enzyme production resources. The homeostatic constraint limits large changes in metabolite concentrations in the model to avoid their potential impact on other reactions not included in the kinetic model but

present in the living organism. The constraints were applied and optimizations were carried out using COPASI software. Several kinetic models were used. Experiments revealed that a homeostatic constraint caused heavier objective function value decrease than the total enzyme activity constraint. Both constraints changed the ranks of adjustable parameter combinations in the list of best combinations. No “universal” constraint-independent combinations of adjustable parameters were found suggesting that the mentioned constraints heavily influence the rank of best adjustable parameter combinations and should be applied in the optimization.

17:50 [Min Roh](#)

dwSSA++: efficient rare event probability estimation algorithm with leaping

SPEAKER: [Min Roh](#)

ABSTRACT. As computational tools became more affordable and powerful, there has been an extensive research on the role of stochasticity in biochemical systems, such as in bacteriophage lambda, phenotypical variations in cloned cells, and cell mutations in tumor formation. For these systems, stochastic modeling is necessary to capture the inherent variability of the underlying mechanism. However, many interesting phenomena that require stochastic modeling also involve rarity in that they are not a part of typical system behavior. The number of trajectories required to accurately estimate the probability of a rare event, which is inversely proportional to the probability, can be prohibitively expensive with conventional Monte Carlo simulation techniques. The doubly weighted stochastic simulation algorithm was developed by Daigle et al. to efficiently estimate a rare event probability by combining Rubinstein’s multilevel cross-entropy method into Gillespie’s stochastic simulation algorithm (SSA). The main contribution of this method was that the importance sampling parameters required to propagate the original system toward the event of interest were selected automatically without requiring user insight. The authors demonstrated a significant computational gain over using SSA alone. However, convergence rate of the multilevel cross-entropy method can be slow or non-existent if the system reaches a parametric plateau, where the cross-entropy method is unable to detect sufficient signal due to lack of stochasticity. Locations or existence of such parametric plateau is not known in advance, and the dwSSA does not

provide a way to “leap” through the plateau. In this talk we introduce dwSSA++ that significantly improves the convergence rate of the original dwSSA. The speed up is achieved by integrating a modified version of the cross-entropy leaping that was first introduced in Stochastic Parameter Search for Events++ (SParSE++) by Roh et al. We compare the performance of dwSSA and dwSSA++ using a Susceptible-Infectious-Recovered-Susceptible (SIRS) disease dynamics model as well as a yeast polarization model.

18:10 [Gang Liu](#), [Jarcy Zee](#), [Lisa Henn](#), [Joshua Shimony](#), [Anca Stefan](#), [Brenda Gillespie](#), [Robert Merion](#) and [Victor Andreev](#)

Clustering Biological Systems Using Correlation Matrices

SPEAKER: [Gang Liu](#)

ABSTRACT. Correlation matrices describing variable interdependency in biological systems provide valuable information about systems’ structures and functions. Sometimes, the interdependence is even more critical for differentiating biological system subtypes than commonly used characteristics, such as levels of omics, images, or other biological markers and attributes. There is an increasing need to use correlation matrices representing interdependence as signals for identifying patterns within biological systems. However, cluster analysis methods using correlation matrices have received little attention. We propose to use the upper-triangle elements of a correlation matrix to form a “snake vector” representing the entire correlation matrix. Then we cluster “snake vectors” by using existing clustering methods. We benchmark our method with existing methods for comparing correlation matrices, such as random skewers, T statistics, and S statistics, which focus on calculating the distances among the correlation matrices. Importantly, these existing methods only allow the use of hierarchical clustering based on pairwise distances between matrices. One advantage of our proposed method, which transforms correlation matrices into vectors, is the ability to apply a variety of standard clustering algorithms (e.g., K-means, K-medoids and hierarchical). Furthermore, a “snake vector” can be concatenated with the mean and variance of each attribute to form a “dragon vector” that synchronously leverages both levels of attributes and their interdependencies. We tested our method by clustering fMRI brain images from

young and old individuals using connectivity matrices (correlations of brain signals across brain regions). The misclassification error of 2.7% using our proposed “snake vector” method outperformed the three existing methods (each with >40% misclassification error). In a simulation study, we derived two groups of matrices from two prototypes representing substantially different brain connectivity matrices. We also obtained smaller misclassification errors using our method compared to using existing methods, which demonstrated the superiority of “snake vectors” method for clustering correlation matrices.

16:30-18:30 Session 19C: Parallel Session VI c:
Cellular Variability

CHAIR: [Young Cao](#)

LOCATION: Old Dominion Ballroom

16:30 [Hao Ge](#), [Hong Qian](#) and [Xiaoliang Sunney Xie](#)
Nonequilibrium stochastic dynamics at single cell level
SPEAKER: [Hao Ge](#)

ABSTRACT. Stochastic processes become more and more popular to model the mesoscopic nonequilibrium biophysical dynamics, which well fit the recent development of advanced experimental techniques at single-cell level.

Here I will take about two short stories. One is the molecular mechanism of transcriptional burst, which is uncovered by combining single-molecule in vitro experiments and stochastic models. The other is a new rate formula for phenotype transition at the intermediate region of gene-state switching for single cells, which is more general and more close to the reality of living cells. The new rate formula can explain a "noise enhancer" therapy for HIV reported recently, which motivated a future project of us.

16:50 [Uchenna Anyaegbunam](#), [Silke Hauf](#) and [Stefan Legewie](#)

Evaluating the Robustness of the Temporal Order of Anaphase Events using an Ensemble of Single Cell Models

SPEAKER: [Uchenna Anyaegbunam](#)

ABSTRACT. Temporally ordered progression through a series of molecular events is essential for the successful completion of the cell cycle. Particularly, the splitting of chromosomes during anaphase needs to be coordinated with changes in the spindle apparatus, and with reversal from

the mitotic to the interphasic state [1-4]. Here we address the question of how cellular heterogeneities (such as cell-to-cell variation in the abundance of anaphase regulatory proteins like securin and cyclin B) affect the relative timing of chromosome splitting and mitotic exit, with the aim of predicting mechanisms of temporal robustness. To this end, we extended an existing cell population average model, which describes the dynamics of anaphase regulatory proteins [5], to an ensemble of single cell models by sampling the protein concentrations from a lognormal distribution. This allows us to adequately represent cell-to-cell variation. This model is then calibrated by fitting to single cell data of wild type and perturbed cells. The single cell model reproduces the experimentally observed robustness of temporal order in wild type cells. For certain perturbation conditions, it predicts subpopulations of cells that exhibit problems in the temporal coordination of anaphase events, with possible implications for genomic instability. These predictions could be tested by assessing cell cycle completion under novel perturbation experiments, in which anaphase regulatory proteins are downregulated or overexpressed. Analysis of our model together with single cell data will aid in determining how genetically stable and unstable subpopulations differ in their protein content. Taken together, our results provide insights into the buffering of heterogeneity that ensures genome stability.

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17:10 [Zhaleh Ghaemi](#) and [Zaida Luthey-Schulten](#)
mRNA Production Noise in Eukaryotic Cells
SPEAKER: [Zhaleh Ghaemi](#)

ABSTRACT. An important component of the transcription process in eukaryotic cells is RNA splicing accomplished by the spliceosome. The Spliceosome is a complicated and highly dynamic machine that removes introns from precursor mRNA (pre-mRNA) and produces the mRNA. It consists of five protein–RNA complexes in the form of small nuclear ribonucleoproteins (snRNP).

We study the sequential formation of each snRNP, the assembly of the spliceosome, the removal of introns and the production of mRNAs in spatially-resolved models of a yeast and human cells. Specifically, using whole-cell simulations, we evaluate the noise associated with each of these processes under variable physiological conditions which ultimately leads to mRNA production noise. In addition, because determining the exact geometry of cellular components using experiments is a challenging task, we explicitly estimate the noise produced by the varying geometry in a population of eukaryotic cells. We start with the formation of a snRNP from its components. We have derived a series of kinetic equations that describe the assembly process of snRNPs. Preliminary results from this kinetic model in our *S. cerevisiae* and Hella cell geometries show that we can successfully generate the most abundant component of spliceosome, and observe the noisiness of its formation at different cellular RNA and protein (as reacting species) counts. The simulated time scale of snRNP particle formation compares well with experimental results, serving to validate our model.

These simulations can lay the foundation for studying eukaryotic systems with spatial resolution and pathogen-related processes such as alternative splicing in detailed models.

17:30 [Ryan Suderman](#), [John Bachman](#), [Adam Smith](#),
[Peter Sorger](#) and [Eric Deeds](#)
Fundamental Trade-offs between Information Flow in Single Cells and Cell Populations
SPEAKER: [Ryan Suderman](#)

ABSTRACT. Signal transduction networks allow eukaryotic cells to make decisions based on information about intracellular state and the

environment. Biochemical noise significantly diminishes the fidelity of signaling: networks examined to date appear to transmit less than 1 bit of information. It is unclear how networks that control critical cell fate decisions (e.g. cell division and apoptosis) can function with such low levels of information transfer. Here, we employ theory, experiments and numerical analysis to demonstrate an inherent trade-off between the information transferred in individual cells and the information available to control population-level responses. Noise in receptor-mediated apoptosis reduces information transfer to approximately one bit at the single-cell level but allows 3-4 bits of information to be transmitted at the population level. For processes such as eukaryotic chemotaxis, in which single cells are the functional unit, we find high levels of information transmission at a single-cell level. Thus, low levels of information transfer are unlikely to represent a physical limit. Instead, we propose that signaling networks exploit noise at the single-cell level to increase population-level information transfer, allowing extracellular ligands, whose levels are also subject to noise, to incrementally regulate phenotypic changes. This is particularly critical for discrete changes in fate (e.g. life vs. death) for which the key variable is the fraction of cells engaged. Our findings provide a framework for rationalizing the high levels of noise in metazoan signaling networks and have implications for the development of drugs that target these networks in the treatment of cancer and other diseases.

18:30-20:30 Session : Poster Session II

We ask all posters be displayed in both poster sessions.
For poster presentation, please check the poster presentation assignment page for detailed poster numbers.

LOCATION: Commonwealth Ballroom

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ICSB 2017: INTERNATIONAL CONFERENCE ON SYSTEMS BIOLOGY 2017

PROGRAM INDEXES

PROGRAM FOR FRIDAY, AUGUST 11TH

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08:30-10:30 Session 20: Friday Morning

CHAIR: [Xueyang Feng](#)

LOCATION: Colonial Hall

08:30 [Ursula Kummer](#)

COPASI – Application in research and training

SPEAKER: [Ursula Kummer](#)

ABSTRACT.

COPASI is a software for computational systems biology that is and has been developed as a joint venture of the groups of Pedro Mendes (now at University of Connecticut) and my own group since the year 2000. During these years COPASI has integrated standard, as well as newly developed algorithms to model, simulate and analyse biological processes in many different ways. Thus, COPASI supports e.g. both ODE-based as well as stochastic (discrete particle based) formalisms. In addition, COPASI features include steady state calculation, sensitivity analyses, optimization, parameter fitting, parameter scanning and computing features of nonlinear dynamical systems such as Lyapunov exponents, among others. COPASI houses new developments, e.g. in the area of hybrid approaches, parameter estimation, complexity reduction and nonlinear dynamics. In essence, we use COPASI as a platform in which we integrate new algorithms and methods once they are validated and relatively stable to use.

Due to the fact that the basic features are simple to use, the software is also often used in the training of systems biologists around the world. However, the software is certainly not restricted to basic, simple features and advanced features are used in many different research projects.

The talk will briefly summarize the features of the software and will then concentrate on recent advanced developments and their application in

research. Finally, one example application on the multi-scale modeling of NFkB signalling in hepatocytes is described in more detail.

09:00 [Edda Klipp](#)

Systematic integration of models and data for yeast growth and division

SPEAKER: [Edda Klipp](#)

ABSTRACT. With the progress of genome-wide experimental approaches we witness the establishment of more and more libraries of genome-wide data for proteins or RNA or metabolites. However, the separated consideration of metabolic networks or gene regulation networks does not tell us how these networks are integrated to allow a cell to grow, divide and respond to changing environments.

We use the yeast *Saccharomyces cerevisiae* as the model organism for eukaryotic cells allowing to comprehensively analyzing regulatory networks and their integration with cellular physiology. We use a modular and iterative approach that allows for a systematic integration of cellular functions into a comprehensive model allowing to link processes that are strongly interlinked in cellular life, but measured separately.

09:30 [Coffee Break](#)

Friday Morning Coffee Break

SPEAKER: [Coffee Break](#)

10:00 [The Team Of Jae Kim And Carla Finkielstein](#)

A model-driven experimental approach unveils the interplay between the circadian factor Period 2 and the tumor suppressor p53.

SPEAKER: [The Team Of Jae Kim And Carla Finkielstein](#)

ABSTRACT. In addition to coordinating the body's physiological and metabolic functions, the circadian (~24h) core clock mechanism exerts a multilevel regulation of the cell division process. This is particularly relevant when it comes to the mechanism by which circadian factors, such as PER2, modulate the cellular response to genotoxic stress that leads to cell cycle arrest. We have previously reported that PER2 directly interacts with the C-terminus domain of p53 promoting p53's stabilization. Interestingly, PER2 binding to p53 prevents p53 oligomerization and its transcriptional activity in response to genotoxic

stress. Unexpectedly, the expression peaks of PER2 and p53 were found out-of-phase in total extracts, a result that was in sharp contrast with the predicted stabilizing role of PER2 on p53. In this talk, we will illustrate how these unexpected phase relationships were analyzed by using systematic modeling of all possible regulatory scenarios to predict the ou-of-phase relationship between PER2 and p53 were possible under conditions in which i) PER2 association to p53 favors p53's nuclear entry and where ii) PER2 was able to bind to various ubiquitinated forms of p53. Model predictions were validated by findings that showed p53 half-life was increased in the nucleus compared to the cytosol compartment and its localization modulated by endogenous PER2 levels. Thus, overexpression of PER2 drove p53 to the nucleus whereas PER2 depletion by siRNA prevented p53's nuclear accumulation. These results were further supported by in vitro binding assays that confirmed PER2 binding to p53 occurred independently of p53's ubiquitination status. In summary, our work illustrates how clock regulatory nodes can be inferred from oscillating time course data with the combination of mathematical modeling and experimental work.

10:30-12:30 Session 21A: Parallel Session VII a:
Systems Biology Education

CHAIR: [John Tyson](#)

LOCATION: Colonial Hall

10:30 [John Tyson](#)

**The Undergraduate Degree in Systems
Biology at Virginia Tech**

SPEAKER: [John Tyson](#)

ABSTRACT. In 2016 Virginia Tech opened a new undergraduate B.S. degree in Systems Biology. In this presentation, I will explain the basic goals, scope and curriculum of the degree, and some of our experiences so far in delivering content to the first two cohorts of the major. The core of the degree consists of the following courses: SYSB 2025-26: Introduction to Systems Biology (3C-3C) SYSB 3035-36: Systems Biology of Genes and Proteins (4C-4C) SYSB 3115-16: Network Dynamics & Cell Physiology (4C-4C) SYSB 4065-66: Research Experience in Systems Biology (4C-4C) SYSB 4135-36: Professional Development in Systems Biology (2C-2C) My intention is to stimulate discussion on the desirability and feasibility of undergraduate degree programs in systems biology at

universities around the world.

10:40 [Thomas Höfer](#)

Systems biology education – When to start?

SPEAKER: [Thomas Höfer](#)

ABSTRACT. Research in systems biology requires knowledge and skills that are traditionally taught in very different curricula (e.g., physics or mathematics versus biology). To address this problem, master's degree courses have been set up. By comparison, courses that teach the foundations of systems biology at the bachelor level have remained rare. Drawing on my experiences as a student of such a degree course and as a university teacher, I will argue that this direct path to systems biology has distinct advantages – for both students and professors.

10:50 [Brian Ingalls](#)

Educational experiences in systems and synthetic biology: a mathematician's perspective

SPEAKER: [Brian Ingalls](#)

ABSTRACT. In this talk I will relate my experiences teaching systems and synthetic biology to interdisciplinary audiences at the University of Waterloo. In 2004, I developed an undergraduate course in differential equation-based kinetic modelling for an audience from Science, Engineering, and Mathematics programs. The course presumes minimal mathematical prerequisites, focusing on development of models and interpretation of analysis, rather than on the details of analytic techniques. I worked my lecture notes into a textbook, which was published as "Mathematical Modelling in Systems Biology: an introduction". Since 2005, I've had the opportunity to present these modelling techniques in the context of synthetic biology in workshops in Toronto and Alberta, to our Waterloo iGEM teams, and in an undergrad Synthetic Biology Design course I co-teach. Mathematical modelling is often unfamiliar to life scientists working in systems and synthetic biology, and so communicating the potential — and the limitations — of these tools remains an important educational challenge.

11:00 [Edda Klipp](#)

TBA

SPEAKER: [Edda Klipp](#)

11:05 [Tomas Helikar](#)

TBA

SPEAKER: [Tomas Helikar](#)

11:10 [All Participants And Speakers](#)

Discussion for Systems Biology Education

SPEAKER: [All Participants And Speakers](#)

10:30-12:30 Session 21B: Parallel Session VII b:
Regulatory Network II

CHAIR: [Bela Novak](#)

LOCATION: Room 342 in Squires

10:30 [Heather Deter](#), [Nicholas Butzin](#), [Roderick Jensen](#)
and [William Mather](#)

**Analysis and classification of differential
production within toxin-antitoxin systems
using large datasets**

SPEAKER: [Heather Deter](#)

ABSTRACT. Toxin-antitoxin (TA) systems are key regulators of bacterial persistence, a multidrug-tolerant state found in bacterial species that is a major contributing factor to the growing human health crisis of antibiotic resistance. Type II TA systems consist of two proteins, a toxin and an antitoxin; the toxin is neutralized when they form a complex. The ratio of antitoxin to toxin is significantly greater than 1.0 in the non-persister state, but this ratio is expected to become smaller during persistence. Analysis of multiple datasets (RNA-seq, ribosome profiling) and results from translation initiation rate calculators reveal multiple mechanisms that ensure a high antitoxin to toxin ratio in the non-persister state. The regulation mechanisms include both translational and transcriptional regulation. We classified E. coli type II TA systems into four distinct classes based on the mechanism of differential protein production between toxin and antitoxin. We find that the most common regulation mechanism is translational regulation. This classification scheme further refines our understanding of the fundamental mechanisms underlying bacterial persistence, especially regarding maintenance of the antitoxin to toxin ratio.

10:50 [Julia Kamenz](#), [Tamara Mihaljev](#), [George Murray](#),
[Saahil Golia](#), [Tatiana Boluarte](#), [Stefan Legewie](#)
and [Silke Hauf](#)

**Exploring the dynamic regulation underlying
synchronous chromosome splitting in
anaphase**

SPEAKER: [Silke Hauf](#)

ABSTRACT. When cells divide, they undergo an ordered series of events, called the cell cycle.

The regulatory pathways that govern major transitions within the cell cycle typically contain positive feedback loops, which ensures that the transition occurs quickly and is irreversible. One important step within the cell cycle is anaphase: chromosomes split abruptly and synchronously to move into the emerging daughter cells, which is triggered by the protease separase. Any error in this step can lead to abnormal chromosome numbers in the daughter cells, a condition observed in cancer cells. Whether the abrupt and faithful splitting of chromosomes in anaphase necessitates positive feedback regulation is unclear. We systematically analyzed the dynamics of sister chromatid separation in fission yeast at the single-cell level. All chromosomes split during a narrow time window. Separase activity and the degradation kinetics of its inhibitor, securin, are the main determinants of this synchronicity. Mathematical modelling on the basis of our findings suggests that synchronicity is established in the absence of feedback regulation. Simple assumptions about securin-separase association and securin degradation are sufficient to explain rapid separase release and abrupt chromosome splitting. Hence, chromosome splitting, being already irreversible by nature, may be one of the few major cell cycle transitions that can operate without positive feedback.

11:10 [Xiao Gan](#) and [Reka Albert](#)

Analysis of a dynamic model of guard cell signaling reveals the stability of signal propagation

SPEAKER: [Xiao Gan](#)

ABSTRACT. Analyzing the attractors of dynamic models of biological systems can provide valuable insight into biological phenotypes. To find out the best methods of attractor analysis of dynamical systems with a large state space, we identified the attractors of a multi-level, 70-node dynamic model of the stomatal opening process in plants, with state space of $\sim 10^{31}$. We first reduced unregulated nodes and simple mediator nodes, and then simplified the regulatory functions of selected nodes. Next, we performed attractor analysis on the resulting 32-node reduced model by three methods. First, we converted the model into a Boolean model, then applied two attractor-finding algorithms, stable motif and GINsim. The stable motif based method computes all attractors of a Boolean model including all possible oscillations; GINsim computes all steady states and confirms

oscillations by simulation. Second, we performed theoretical analysis of the regulatory functions, validating the attractor conclusions and extending the conclusions to perturbed cases. Third, we extended the stable motif method from Boolean to multi-level and apply it. The method is based on an expanded representation of the network that incorporates all the regulatory functions, by introducing virtual nodes for each state of an original node and composite nodes that express the ‘And’ Boolean operation. Stable motifs, subgraphs whose nodes’ states can stabilize on their own, can then be identified from the topology of the expanded network, leading to reduction of the network and identification of attractors (see Figure 1). Combining the results of all three methods, we concluded that all nodes except two in the reduced model have a single attractor; and only two nodes can admit oscillations. The multistability or oscillations of these four nodes do not affect the stomatal opening level in any situation. The high degree of attractor similarity shows stability of signal propagation, despite the complex structure of the network.

11:30 [Ron Henkel](#), [Fabienne Lambusch](#), [Dagmar Waltemath](#) and [Wolfgang Müller](#)
Identifying frequent patterns in biochemical reaction networks using graph-mining
SPEAKER: [Ron Henkel](#)

ABSTRACT. Background: It is common practice to represent molecular and cell biological processes as biochemical reaction networks using computational methods. Such models can be studied, analysed, and compared to improve our understanding of biology. One possible similarity measure for biological reaction networks is the occurrence of similar structures, including motifs, in the networks’ computational representation. The large number of models available from open model repositories, such as BioModels or the Physiome Model Repository, demands automated methods to support researchers in the identification of recurring patterns and in the recognition of biologically relevant motifs within a set of potentially interesting models. Specifically, for the problem of finding patterns in large, sparsely connected networks only partial solutions exist.

Result: We propose a workflow to identify frequent structural patterns in biochemical reaction networks encoded in the Systems

Biology Markup Language (SBML, [1]). To detect such patterns, we implement a sub-graph mining algorithm. Once patterns are identified, the textual pattern description can automatically be converted into a graphical representation easily understandable for a user. Furthermore, information about the pattern distribution among the selected set of models can be retrieved. The workflow can be applied to a custom set of models or to models already existing in our graph database MaSyMoS [2]. The workflow was validated with 575 models from the curated branch of BioModels [3]. As a showcase, we highlight interesting and frequent structural patterns that appear within this model set. We further provide exemplary patterns that incorporate terms from the Systems Biology Ontology (SBO, [4]).

Conclusions: The occurrences of frequent patterns may give insight into central biological processes, evaluate biological motifs, or serve as a similarity measure for models that share common structures.

References [1] Hucka, M. et al. "The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models." *Bioinformatics* 19.4 (2003): 524-531. [2] Henkel, R. et al. "Combining computational models, semantic annotations and simulation experiments in a graph database." *Database* 2015 (2015): bau130. [3] Le Novère, N. et al. "BioModels Database: a free, centralized database of curated, published, quantitative kinetic models of biochemical and cellular systems." *Nucleic acids research* 34.suppl 1 (2006): D689-D691. [4] Courtot, M. et al. "Controlled vocabularies and semantics in systems biology." *Molecular systems biology* 7.1 (2011): 543.

11:50 [Pavel Kraikivski](#), [T.M. Murali](#) and [John Tyson](#)
**Cell Cycle Control in Budding Yeast:
Robustness of Model Predictions**
SPEAKER: [Pavel Kraikivski](#)

ABSTRACT. We have recently crafted a new mathematical model of cell cycle progression in yeast that successfully explains the observed phenotypes of 257 budding yeast mutant strains. The model can be used to predict the phenotypes of novel combinations of mutant alleles and the number of such predictions is estimated to exceed the experimentally tested combinations by the order of 1.0e5. Thus, prioritizing

predictions for experimental validation is an important step before starting expensive wet lab tests. We have developed an automated method to search for many alternative parameter sets that are consistent with experimental data and use those sets to explore the dependence of predictions on choice of parameters. We start with a “basal” parameter set that is consistent with 257 experimentally characterized mutants and search for alternative parameter sets by randomly perturbing all parameters simultaneously, retaining only those sets that are consistent with a selected set of 90 most informative mutant strains. We have found ~1000 alternative parameter sets for our model of cell cycle regulation, each parameter set can be thought as an alternative model that is also capable to explain a set of experimental data. Performing sensitivity analysis we have categorized selected predictions as robust if models with alternative parameter sets produce mostly the same results as the model with the “basal” set, or fragile otherwise. Furthermore, principal component analysis demonstrates tight fitting of the model to experimental data, contradicting the popular opinion that all systems biology models are universally “sloppy” in fitting data. Robust predictions depend on the regulatory network itself rather than specific parameter values and thus future experimental tests of robust predictions will either confirm the underlying molecular mechanism or provide new insights into how the cell division cycle is regulated. Fragile predictions are sensitive to values of adjustable parameters and thus their experimental characterization will be useful to constrain adjustable parameters of the model.

12:10 [Caterina Thomaseth](#), [Dirk Fey](#), [Tapesh Santra](#),
[Oleksii Rukhlenko](#), [Boris Kholodenko](#) and [Nicole Erika Radde](#)

Evaluating the effects of measurement noise on the inference of biological regulatory networks using Modular Response Analysis

SPEAKER: [Caterina Thomaseth](#)

ABSTRACT. Modular Response Analysis (MRA) is a powerful mathematical framework, which allows to unravel the topology of intracellular regulatory networks from consecutive perturbation experiments. This method relies on steady state measurements of relevant species of the investigated network. MRA is widely used in systems biology, including topology estimation from Western blot data, which are known to be quite noisy. The calculation of connection

coefficients describing the network's interactions requires the solution of a reverse problem, which may be unstable with respect to noisy data.

In this study, we investigate how errors affect network inference using MRA and its robustness with respect to noise. Uncertainty in the input data propagates in a nonlinear manner to affect the variability of the inferred coefficients, producing possibly incorrectly inferred topologies. Through an extensive *in silico* study of models of two well-known biological systems, MAPK and p53, we compare different methodologies and computational approaches to handle noisy data in the inference process. We look at different perturbation strengths, different replicates' numbers, and we solve the reverse problem using either ordinary or total least squares.

Our results demonstrate that it is not obvious which MRA formulation provides more accurate solutions, in terms of bias and variance of the inferred coefficients, and even small measurement noise can lead to erroneous results. Nonlinear dependencies of the equilibria of the system with respect to perturbed parameters can lead to biased estimators of the connection coefficients. Results differ for the two models, having different degrees of such nonlinearities. Nevertheless, the correct experimental design and MRA formulation maximise the probability of a correctly inferred topology.

The proposed analysis brings a deeper understanding of the effects of noisy data on regulatory networks inference via MRA, demonstrating that the choice of experimental design and MRA formulation is crucial for a reliable topology estimation.

10:30-12:30 Session 21C: Parallel Session VII c:
Computational Methodology III

CHAIR: [Tm Murali](#)

LOCATION: Brush Mountain A & B

10:30 [Matěj Troják](#), [David Šafránek](#), [Jakub Hrabec](#),
[Matěj Hajnal](#), [Jakub Šalagovič](#), [Františka Romanovská](#) and [Jan Červený](#)

E-cyanobacterium.org: A Web-based Platform for Systems Biology of Cyanobacteria

SPEAKER: [Jan Červený](#)

ABSTRACT. E-cyanobacterium.org is an online platform providing tools for public sharing,

annotation, analysis, and visualization of dynamical models and wet-lab experiments related to cyanobacteria. The platform is unique in integrating abstract mathematical models with a precise consortium-agreed biochemical description provided in a rule-based formalism. The general aim is to stimulate collaboration between experimental and computational systems biologists to achieve better understanding cyanobacteria. We developed the tool that focuses on providing a general online platform for systems biology of cyanobacteria unifying the state-of-the-art knowledge base, related kinetic models and wet-lab experiments. In contrast to existing tools such as Biomodels.net or CellML, which provide general repositories for biological models, e-cyanobacteria.org is directly focused on cyanobacteria organisms. Our platform provides a unique solution based on integrating the well-acknowledged systems biology standards with advanced computer scientific techniques targeting the mentioned issues. Moreover, using in silico experiments for estimation of optimal culturing conditions and runtime multi-parameter optimization of variable environmental parameters can help to simplify optimization of real biotechnological applications, both on the side of cell biology and photobioreactors design. Current version is available at <http://www.e-cyanobacterium.org/> and includes the following functions:

- Biochemical Space – formal representation of elemental reactions facilitated by cyanobacteria biochemical entities, the representation is systematically organized by reflecting the hierarchy of biochemical processes ranging from the environment to the cell compartments and accompanied with
- Biochemical Space Language – rule-based formal language;
- Computational Models – repository of stoichiometric and kinetic models providing simulation and static analysis;
- SBML Compatibility – models projected onto the Biochemical Space can be exported into well-annotated SBML files;
- Wet-lab Experiments – import and storage of time-series experiments, relation to models;
- Annotation – detailed annotation of all system components reflecting annotation standards (OBO, OWL);
- Content Visualization (Biochemical Space in means of process hierarchy schemas and modelling/experimental data).

In the current version, the following processes of cyanobacteria are covered: environmental processes, respiration and photosynthesis, circadian clock and metabolism. Environmental processes focus

on precise positioning of cyanobacteria into the context of its environment. Since the website primarily targets in vitro cultivation conditions in a bioreactor, we have compiled relevant elemental reactions. Processes of respiration and photosynthesis cover the energetic components of cyanobacteria. Circadian clock forms core of cyanobacteria and drives most important processes. Above these cellular processes, the metabolic part of the Biochemical Space forms a backbone that connects the bioenergetic components with metabolome and connects all key cellular processes with the general processes occurring in the environment. Currently available tools mostly do not provide sufficient means of supporting entire systems biology workflow. Especially, this applies to existing domain-specific tools devoted to cyanobacteria. Therefore, we believe that our web service makes a significant contribution. For future work, we plan to improve the mapping between mathematics and biology, to enhance the website with more analysis tools, and to automatize the comparison of models against experimental data. Moreover, biochemical space of cyanobacteria is continuously being extended and improved with interactive visualizations of reaction networks based on formal description provided in Biochemical Space Language.

10:50 [Abdul Salam Jarrah](#)

Reverse-Engineering Gene regulatory Networks as Threshold Boolean Networks

SPEAKER: [Abdul Salam Jarrah](#)

ABSTRACT. Inferring the topology and dynamic of gene regulatory networks from data (time-course, input-output, or steady states) is one of the challenging problems in systems biology. Given time course experimental data, the objective is to identify the structure of the network as well as the rules of interaction among the genes of the network. However, even within the Boolean network framework, there usually are many Boolean networks that explain the available data. The so-called threshold Boolean networks(TBNs), initially developed to study neural networks, have been used to model a variety of gene regulatory networks. In a TBN, the future state of each node is determined based on a threshold and a linear combination of the current states of its neighbors. In this talk, we present an algorithm for identifying all threshold network models that reproduce a given Boolean dataset. Our method is rooted in algebraic combinatorics.

11:10 [Jungsik Noh](#), [Mihai Azoitei](#), [Philippe Roudo](#),
[Klaus Hahn](#) and [Gaudenz Danuser](#)
**GEF-H1 regulation by microtubule dynamics
unveiled by fluctuation analysis of biosensor
images**
SPEAKER: [Jungsik Noh](#)

ABSTRACT. RhoA GTPase is a signaling molecule implicated in orchestrating cytoskeleton dynamic processes such as actin assembly and actomyosin contractility. Its activity is regulated by several guanine exchange factors, of which one, GEF-H1, is thought to localize in a non-activating state to microtubules (MTs). By acute pharmacological induction of MT disassembly across the entire cell it was shown that RhoA is activated in a GEF-H1 dependent fashion. This suggests that GEF-H1 mediates an important link between MT and actin network dynamics. However, these previous whole-cell perturbation studies have left unanswered whether local MT dynamics drives changes in GEF-H1 activation. This would establish a pathway for MT-actin regulatory cross-talk at the micron and second length and time scales, respectively. To test this possibility we analyzed the subcellular dynamics of GEF-H1 activity in response to MT disassembly events using the spontaneous fluctuation in GEF-H1 activity imaged by a novel biosensor design in conjunction with MT +TIP particle tracking of MT growth. We developed a novel statistical framework to test the hypothesis that the discrete and sparse MT disassembly events modulate the continuous GEF-H1 signal. Overall, GEF-H1 biosensor images exhibited higher activity near the cell edge and shadows along the shafts of MTs confirming that GEF-H1 sequestration by MTs indeed causes deactivation, whereas release from disassembling MTs at the cell periphery may trigger GEF-H1 activation. Indeed, we found that subcellular signals of GEF-H1 activity tend to increase after MT disassembly events with a delay of about 10 sec in breast cancer cells. Our analysis also suggested that MT assembly deactivated GEF-H1 along growth trajectory. On analytical side, to our knowledge this work is the first to statistically couple discrete molecular events to the continuous output of a molecular population.

11:30 [Yuta Tokuoka](#), [Noriko Hiroi](#), [Tetsuya Kobayashi](#),
[Kazuo Yamagata](#) and [Akira Funahashi](#)
**Segmenting four-dimensional fluorescence
microscopic image using Convolutional**

Neural Network

SPEAKER: [Yuta Tokuoka](#)

ABSTRACT. To segment microscopic images is one of the important tasks for quantitative analysis of biological phenomena. The problem of segmentation in biological imaging is that the parameter value of each image processing should be determined beforehand, and the parameter value depends on the feature of each image and imaging conditions. Recently, many studies have been reported which applied Convolutional Neural Network (CNN) for segmenting two-dimensional microscopic image to solve this problem. However, because it is common to acquire multi dimensional microscopic images along with the development of imaging technology, proposals of segmenting multi dimensional microscopic images are desired. In this study, we propose the segmentation algorithm for four-dimensional fluorescence microscopic images using CNN. We implemented an algorithm to segment nuclei from four-dimensional fluorescence microscopic images of mouse embryos using CNN. In dataset creation, we cropped one time point in the three-dimensional fluorescence microscopic image of 4 cell stage of the mouse embryo, and the Ground Truth was created manually. We also interpolated the microscopic image and the Ground Truth in order to match the actual scale. In the implementation of the learning model, segmentation algorithm was implemented based on CNN. Four-dimensional fluorescence microscopic images of 2 to 14 cell stages were used for the evaluation of segmentation. With the current implementation, the voxel accuracy of segmentation achieved 98.74% in average. As a future prospect, we will acquire quantitative indexes from four-dimensional fluorescence microscopic images of early-stage embryos by a further improved segmentation algorithm, and select the most effective indexes to evaluate the quality of embryos.

11:50 [Aditya Pratapa](#), [Neil Adames](#), [Pavel Kraikivski](#),

[John Tyson](#), [Jean Peccoud](#) and [T. M. Murali](#)

CrossPlan: Systematic Planning of Genetic Crosses to Validate Mathematical Models

SPEAKER: [Aditya Pratapa](#)

ABSTRACT. Mathematical models of cellular processes can systematically predict the phenotypes of novel combinations of multi-gene mutations. Searching for informative mutants and

prioritizing them for experimental validation is challenging since the number of possible combinations grows explosively. Moreover, keeping track of the genetic crosses needed to make new mutants and planning sequences of experiments is unmanageable when the experimenter is deluged by hundreds of potentially informative predictions to test.

We present CrossPlan, an algorithm for systematically planning genetic crosses to make a set of target mutants from a set of source mutants. We base our approach on a generic experimental workflow used in performing genetic crosses in budding yeast. CrossPlan uses an integer-linear-program (ILP) to maximize the number of target mutants that we can make under certain experimental constraints.

We apply our method to a comprehensive mathematical model of the protein regulatory network controlling cell division in budding yeast. The number of target mutants we can plan increases linearly with the number of batches planned. We also extend our solution to incorporate other experimental conditions such as a delay factor that decides the availability of a mutant and genetic markers to confirm gene deletions. Our analyses reveal that incorporating the requirement that each gene deletion be associated with a unique marker has only a marginal effect on the number of planned mutants. Our method outperforms a greedy method that plans batches one at a time. Interestingly, planning two or three batches at a time is nearly as optimal as planning all batches simultaneously. The experimental flow that underlies our work is quite generic and our ILP-based algorithm is easy to modify. Hence our framework should be relevant in mammalian systems as well.

12:30-14:00 Session : Friday Lunch

LOCATION: Commonwealth Ballroom

14:00-15:00 Session : Special Session: Career Development in Systems Biology

CHAIR: [Xueyang Feng](#)

LOCATION: Colonial Hall

15:00-16:00 Session : Closing Remarks and Coffee Break

CHAIR: [Young Cao](#)

LOCATION: Colonial Hall