2040 Visions of Process Systems Engineering

Systems approaches in biology and medicine

## **Daehee Hwang**

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### Systems Approaches in Bioengineering

"Gene expression profiling of multiple sclerosis peripheral blood unveils novel biomarkers and links the Rb/E2F pathway with human autoimmunity", Fernando Dangond, Antonio Iglesias, Raul Villanueva, Sandra Camelo, Dianne McKenna-Yasek, Robert H. Brown, George Stephanopoulos, Daehee Hwang, Submitted for publication, *Nature Medicine* (2002).

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"The molecular signature of late-stage human ALS revealed by expression profiling of postmortem spinal cord", F. Dangond, D. Hwang, P. Pasinelli, M.P. Frosch, Geo. Stephanopoulos, Gr. Stephanopoulos, R.H. Brown Jr., and S.R. Gullans. *Physiological Genomics* 16: 229–239 (2004)

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"The molecular signature of late-stage human ALS revealed by expression profiling of postmortem spinal cord gray matter", F. Dangond, D.H. Hwang, S. Camelo, P. Pasinelli, M. P. Frosch, Greg. Stephanopoulos, Geo. Stephanopoulos, R.H. Brown, and S.R. Gullans, *Physiol Genomics*, **16**, 229-239, (2004)

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## **Systems Biology in Early Times**

## Systems Biology - The study of the

mechanisms underlying complex biological processes as integrated systems of many interacting components. Systems biology involves (1) collection of large sets of experimental data (2) proposal of mathematical models that might account for at least some significant aspects of this data set, (3) accurate computer solution of the mathematical equations to obtain numerical predictions, and (4) assessment of the quality of the model by comparing numerical simulations with the experimental data.

First described in 1999 by Leroy Hood



## Systems biology: dynamic network

- Elements (genes, proteins, etc.)- nodes
- Interactions between the elements- edges
- Elements and their interactions are affected by the Context of other systems withincells and organisms
- Interactions between/among elements give rise to the system's Emergent properties



### **Disease Arises from Disease-Perturbed Networks**





### Non-Diseased

### Diseased

## **Current Systems Biology**

- System Perturbation
- Generation of comprehensive global data
- Identification of key molecules
- Network modeling
- Generation of hypotheses
- Validation of hypotheses

## **Resources and tools for systems approaches**

Choi et al., Molecular Plant (2014)

## **Current Systems Biology**

## System Perturbation

- Generation of comprehensive global data Analysis of genomic, proteomic & metabolomics data & data integration.
- Identification of key molecules

Identification of differentially expressed molecules.

Network modeling

Network modeling and analysis for ID of key regulators and pathways.

- Generation of hypotheses
- Validation of hypotheses

### **Development of tools for systems biology**



## iNID database: transcriptome & interactome



### **Developmental signaling pathways**



## Interplays among developmental pathways



## Interplays among developmental pathways

#### Hormone

**Biotic stress** 



ey regulators						
Individual clusters All clusters						
	1 <sup>st</sup> neig	hbors	2 <sup>nd</sup> neigh	2 <sup>nd</sup> neighbors		
cluster	#key regulators	P <sup>c</sup> <sub>1st</sub>	#key regulators	P <sup>c</sup> <sub>2nd</sub>		
1	1	0.9065	1	0.7869		
2	<u>7</u>	0.0319	7	0.0001 *		
3	2	0.3614	2	0.3245		
4	<u>5</u>	0.0214	1	0.4019		
5	1	0.9354	1	0.7587		
6	17	1.51E-17*	15	7.9E-14*		
/	<u>5</u>	2.00292-0	<u>/</u>	3.0E-10		
8	<u>7</u>	0.0002 *	2	0.1053		



# Network models showing Interplays among developmental pathways



### **Development of tools for systems biology**



## GI(GIGANTEA), an Important Modulator of the Core Oscillator of Arabidopsis



#### A model of the plant circadian clock

*Harmer, Annu.Rev.Plant.Biol.*(2009) Kim et al., Nature (2007)

## Mathematical modeling predicts network structure



## Mathematical modeling predicts network structure



## **Experimental confirmation by transgenic plants**



Nuclear and cytosolic GI form incoherent feedforward loop to regulate LHY

## **Application of systems approaches**

### **Application of these tools for various studies**

The utility of these tools has been demonstrated in various systems biology studies.

- Dynamic disease-perturbed networks during the course of prion disease progression Molecular Systems Biology, 2009 & age-related networks of Arabidopsis leaves along the lifespan Science, 2009; Plant Physiology, 2016.
- Construction of RA-associated networks PLOS One, 2012; PNAS, 2015 describing pannus formation, and selection of key regulators of the networks Arthritis and Rheumatism, 2011; JEM, 2012; PNAS, 2014
- Construction of T2D-associated networks, selection of key regulators of the networks Cell Metabolism, 2013; Diabetes, 2015, and elucidation of a retrograde signaling mechanism from the networks Science Signaling, 2012
- Construction of cancer-associated networks Nature Reviews Cancer, 2011 & 2012 and selection of key regulators of the networks JCI, 2012; Oncogene, 2014; Cancer Research, 2016; Nature Communications, 2015; JI, 2015
- Construction of network models related to other diseases, such as AD Cell Death and Differentiation, 2014, PD Nature Communications, 2013, and Interstitial Cystitis Molecular & Cellular Proteomics, 2011, and a metabolic network underlying pharmacokinetics of tacrolimus CPT, 2010.

## Temporal disease-perturbed networks: *Prion disease*



#### Hwang et al., Molecular Systems Biology (2009)

### **Time-evolving cell cycle networks**



Kim et al., Bioinformatics (2014)

### **Application of these tools for various studies**

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## **Mitochondrial disorders**



## A Cybrid model with mtDNA 3243 mutation

#### mtDNA 3243 A>G mutation

Amino acid acceptor stem 3' - OH Pediatric MMC np3303 5' - . G- C MM np 3302 MELAS. DMFD ۰т -т С MELAS np 3291 np 3243 CTCCTTA Dihydrouridine тψс Loop GAGG<sub>TT</sub>C Loop MM np 3250 - C MM np3251 - G - MELAS np 3271 MELAS np 3252 PEM np 3271 G MERRF / MELAS np 3256 TAA Adult MMC np 3260 Anticodon

> Pathological Mutations in tRNALeu(UUR) http://www.mitomap.org/MITOMAP/tRNAleu.pdf Copyright 2002 @ Mitomap.org

#### Peripheral (FR Blood 143B TK<sup>-</sup> cell +Uridine +BrdU Polyethylenglycol 143B ρ<sup>0</sup>-cell +Uridine Platelets (PEG) Fusion +BrdU -uridine Selection +BrdU

Cybrid Model

**Causes 1% of Diabetes** 

Dr. Park (SNU)

Cybrid

## System-level Analysis of Cybrid Models



Chae et al., *Science Signaling* (2013)

## Mutation-load Dependent Differential Expression Patterns





## What Regulates Changes in C3 ?



## Future in systems biology & medicine

## **Multi-dimensional genomic analysis of cancers**



EBV+ Hypermutable Genome-stable High SCNA (Aneuploid)

## **Complementary nature of different omics datasets**



## **Single cell systems biology**



## **Cancer stem cells & drug resistance**

#### **Cellular heterogeneity**

#### **Cancer stem cells & drug resistance**



## Big data analysis

## **Finding relationships**



People You May Know				
Melissa Mays	+1 Add Friend			
Mira Patel	+1 Add Friend			
Sonia Reyes	+1 Add Friend			
Heather Sorensen	+1 Add Friend			
Rebecca Dykes	+1 Add Friend			
Barbara De Maria	+1 Add Friend			
See All				

## **Big data analysis**

## **Finding rules**



how can u		ş.
how can u get herpes		
how can u get hiv		
how can u get aids		
how can u get chlamydia		
how can u get mono		
how can u last longer in bed		
how can u mend a broken her	art	
how can u lose weight fast		
how can u get hpv		
how can u get hepatitis c		
Google Search	Fm Feeling Lucky	



how can an	individual
how can an	individual impact the course of history
how can an	individual make a difference
how can an	individual affect society
how can an	individual change history
how can an	individual
how can an	individual reduce global warming
how can an	individual be supported to reflect on an incident
how can an	individual help to conserve water
how can an	individual influence an organization
how can an	individual buy stock

Google Search

Pm Feeling Lucky

## Other big data problems in proteomics

Finding co-occurring post-translational modifications in the same proteins and other proteins in the same pathway???

Finding frequently co-varying proteins in different pathways (cross-talks between pathways) ???

Finding frequently co-varying network modules (pathways) that can be used as bases for interpretation of a new dataset???

## **Network architecture**



# Happy Birthday !! Happy Retirement !!