# Systems Biology in the Philippines – Past, Present and Potential

## PGC Webinar
## April 19, 2016

Seminar
on
SBML, BioSPICE – Emerging Standards and Platforms for Systems Biology
by
Dr. Eduardo R. Mendoza
Adjunct Professor
Department of Mathematics
University of the Philippines
on
Wednesday, 29 January 2003
10:30 a.m., Audio-Visual Room, Basement
Marine Science Institute

Abstract

*Is Systems Biology just the newest buzzword for getting big bucks (BMBF "Systeme des Lebens" 50 Mio Euro, DARPA Bio-computing 60 Mio $ ...)?*
*In this talk, we discuss how its systems engineering-inspired approach, which is based on intensive use of modeling/simulation and its tight integration with experimental work, can advance our understanding of biological structures and dynamics. A recent example is the use of "elementary mode analysis" (due to S. Schuster, Berlin) to explain and predict key properties of E.coli's metabolic pathways (Stelling et al. Nature 420, Nov 14). "Engineering" bigger, more complex models will also require more collaboration between different research teams as well as the ability to re-use components – this will only be possible if standard frameworks for model definition and exchange are established. We will discuss two emerging standards in this regard:*
- *SBML (Systems Biology Mark-Up Language) an XML-based specification for modeling biochemical networks.*
- *BioSPICE, a modular open source software platform being built in the DARPA Bio-computing Project with the aim of providing bio-scientists a flexible, easy-to-use modeling and simulation environment.*

Molecular BioSystems

PAPER

Stability analysis of the ODE model representation of amyloidogenic processing in Alzheimer's disease in the presence of SORLA†

Jan Harold M. Alcantara,[a] Angelyn R. Lao[*b] and Leonor A. Ruivivar[*c]

1 Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by amyloid plaques in the brains of affected individuals. The increasing incidence of the disease among the human population makes it imperative to continue and intensify efforts to better understand the nature of AD and hopefully find a cure.

A popular hypothesis among medical researchers is known as the amyloid hypothesis.[1] Central to the amyloid hypothesis is the APP, a type-1 membrane protein expressed in many neuronal and non-neuronal cell types.[2,3] The idea is that the onset and progression of the disease are determined by the breakdown of APP to Aβ.

The APP in cells (including the neurons) is processed into different soluble and membrane-associated fragments through two mutually exclusive pathways. The amyloidogenic pathway is of specific importance in AD. In this pathway, APP is cleaved first by β-secretase producing a soluble APP-beta (sAPPβ) peptide and a C99 peptide (the 99-amino acid C-terminal fragment). Further, the C99 peptide is cleaved by gamma-secretase (γ-secretase), and this process results in the production of AICD and amyloid β peptide (Aβ), a 40- to 42-amino acid fragment derived from the extracellular and transmembrane domains of APP). The amyloid hypothesis suggests that the neuronal dysfunction and cell loss in AD are caused by the processing of Aβ into neurotoxic oligomers and senile plaques.[5,6] In the non-amyloidogenic pathway, APP is cleaved first by γ-secretase, and this produces a soluble APP-alpha (sAPPα) peptide and a C83 peptide (the 83-amino acid C-terminal fragment). Further cleavage by β- and γ-secretases produces AICD (APP intracellular domain) and P3 (a 3 kDa fragment composed of residues 17–40 or 17–42 of the amyloid beta peptide). This pathway leads to the destruction of the Aβ peptide.[6,7]

At present, efforts to prevent, interrupt, and cure AD are underway, but drug trials are expensive and take a considerable amount of time since AD progresses very gradually and drug efficacy can only be evaluated after a long period of time.[11] Hence, one of the alternative measures towards the understanding of the disease is to mathematically represent the biochemical system involved in the amyloidogenic process. Modeling the system can provide researchers with a means to

***2003*** ***2016***


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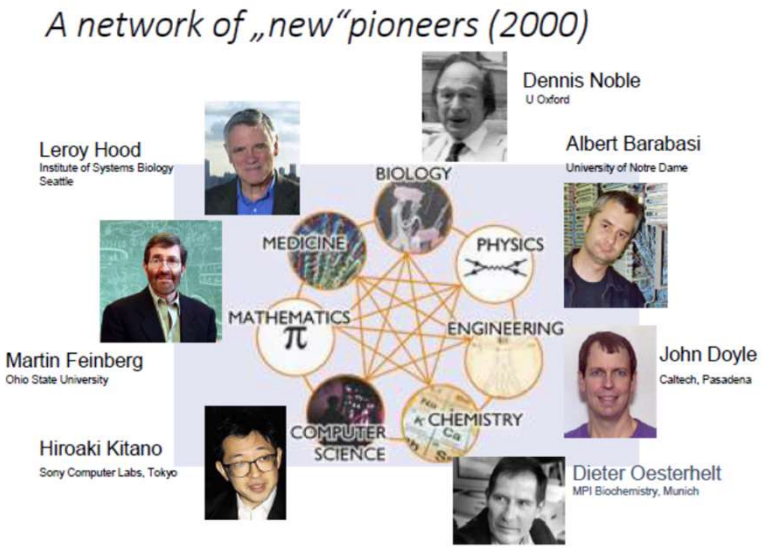
# 2 Quick Remarks

- ***Systems Biology*** *integrates quantitative experimental work and computational modeling to understand structure and dynamics of biological systems in terms of molecular/cellular processes*
  - *(re)emerged ~ 2000 (ISB in Seattle, ICSB in Tokyo, SBML in Pasadena)*
- ***Filipino Systems Biology*** *began with B. Aguda´s cell cycle papers in 1999*




*Proc. Natl. Acad. Sci. USA*
Vol. 96, pp. 11352–11357, September 1999
Cell Biology

**A quantitative analysis of the kinetics of the $G_2$ DNA damage checkpoint system**

BALTAZAR D. AGUDA*

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*Edited by Joan V. Ruderman, Harvard Medical School, Boston, MA, and approved July 19, 1999 (received for review March 29, 1999)*

**Oncogene (1999) 18,** 2846–2851

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**Instabilities in phosphorylation-dephosphorylation cascades and cell cycle checkpoints**

BD Aguda

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**Instabilities in phosphorylation-dephosphorylation cascades and cell cycle checkpoints**

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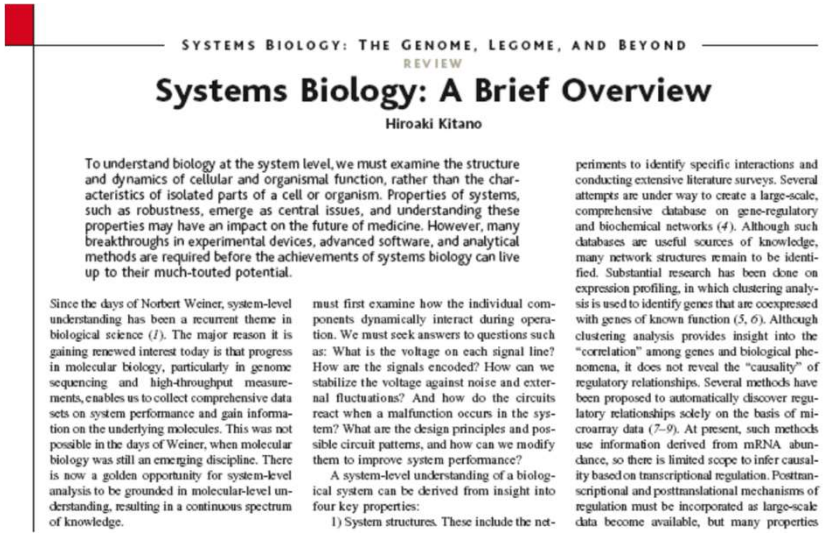
# Topics to be covered


1. *The Past: the First Decade of Systems Biology in the Philippines (2003 – 2013)*
   - *5 Key Characteristics*
   - *Highlights and Results*
2. *The Present: Challenges in a Period of Transition (2014 – present)*
3. *The Potential: some short- and mid-term Opportunities*

# 1. The Past: The First Decade of Systems Biology in the Philippines (2003 – 2013)

*The beginnings*

- ***Oct 2002:*** *move from IT industry to academe (interest in modeling biological networks)*
- *Learned soon from H. Kitano's March 2002 essay in „Science" that this was (part of) „Systems Biology"*
- *Early challenges for SysBio in Phil:*
  - *Generally low level of basic research funding in the country*
  - *Advocating a new (unknown) field, which required a „mind change"*
- *Initial courses at NIMBB and Math Dept in Jan 2003*
- *MCBI (Math and Comp Bio Initiative) launched Mar 2003 – soon renamed MLSI (Math Life Sciences Initiative) to reflect wider scope (e.g. collaboration (coral reef modeling)*



SYSTEMS BIOLOGY: THE GENOME, LEGOME, AND BEYOND

REVIEW

**Systems Biology: A Brief Overview**

Hiroaki Kitano

To understand biology at the system level, we must examine the structure and dynamics of cellular and organismal function, rather than the characteristics of isolated parts of a cell or organism. Properties of systems, such as robustness, emerge as central issues, and understanding these properties may have an impact on the future of medicine. However, many breakthroughs in experimental devices, advanced software, and analytical methods are required before the achievements of systems biology can live up to their much-touted potential.

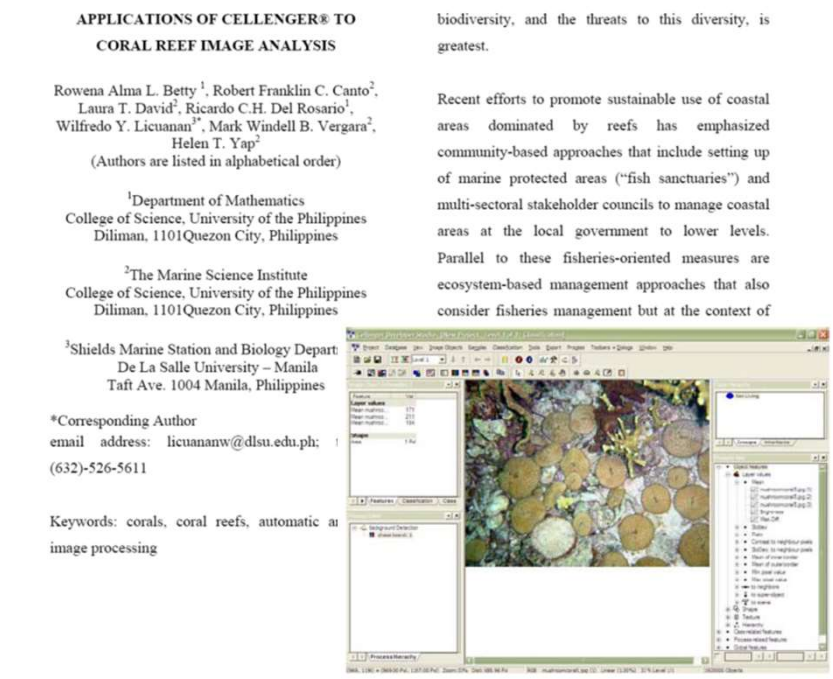
Since the days of Norbert Weiner, system-level understanding has been a recurrent theme in biological science (*1*). The major reason it is gaining renewed interest today is that progress in molecular biology, particularly in genome sequencing and high-throughput measurements, enables us to collect comprehensive data sets on system performance and gain information on the underlying molecules. This was not possible in the days of Weiner, when molecular biology was still an emerging discipline. There is now a golden opportunity for system-level analysis to be grounded in molecular-level understanding, resulting in a continuous spectrum of knowledge.

must first examine how the individual components dynamically interact during operation. We must seek answers to questions such as: What is the voltage on each signal line? How are the signals encoded? How can we stabilize the voltage against noise and external fluctuations? And how do the circuits react when a malfunction occurs in the system? What are the design principles and possible circuit patterns, and how can we modify them to improve system performance?

A system-level understanding of a biological system can be derived from insight into four key properties:

1) System structures. These include the net-

periments to identify specific interactions and conducting extensive literature surveys. Several attempts are under way to create a large-scale, comprehensive database on gene-regulatory and biochemical networks (*4*). Although such databases are useful sources of knowledge, many network structures remain to be identified. Substantial research has been done on expression profiling, in which clustering analysis is used to identify genes that are coexpressed with genes of known function (*5*, *6*). Although clustering analysis provides insight into the "correlation" among genes and biological phenomena, it does not reveal the "causality" of regulatory relationships. Several methods have been proposed to automatically discover regulatory relationships solely on the basis of microarray data (*7*–*9*). At present, such methods use information derived from mRNA abundance, so there is limited scope to infer causality based on transcriptional regulation. Posttranscriptional and posttranslational mechanisms of regulation must be incorporated as large-scale data become available, but many properties



**APPLICATIONS OF CELLENGER® TO CORAL REEF IMAGE ANALYSIS**

Rowena Alma L. Betty [1], Robert Franklin C. Canto[2], Laura T. David[2], Ricardo C.H. Del Rosario[1], Wilfredo Y. Licuanan[3*], Mark Windell B. Vergara[2], Helen T. Yap[2]
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Keywords: corals, coral reefs, automatic a
image processing

biodiversity, and the threats to this diversity, is greatest.

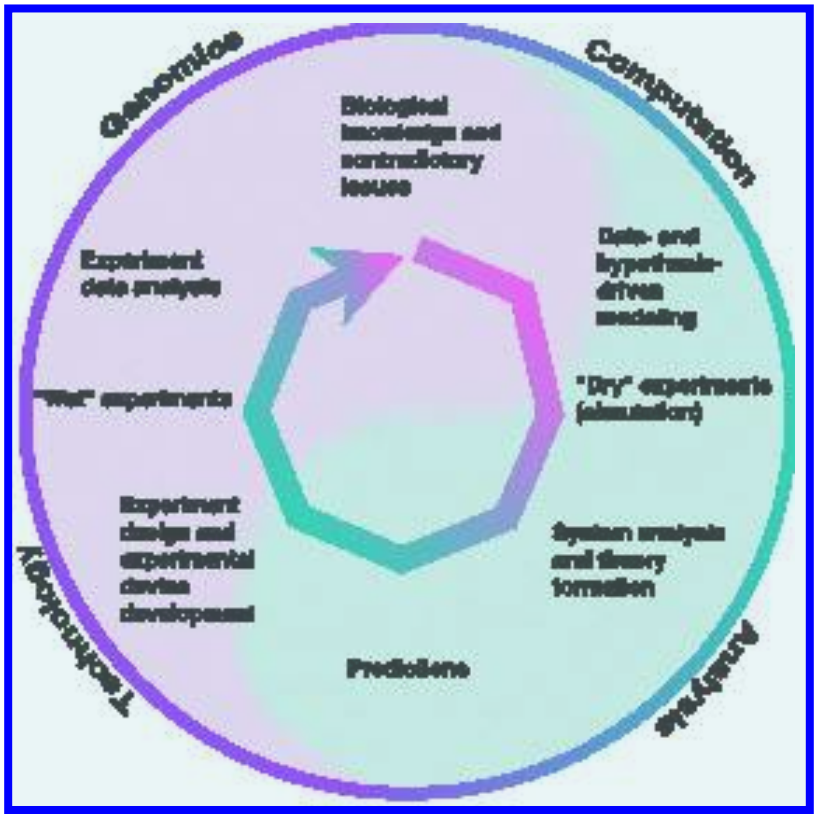
Recent efforts to promote sustainable use of coastal areas dominated by reefs has emphasized community-based approaches that include setting up of marine protected areas ("fish sanctuaries") and multi-sectoral stakeholder councils to manage coastal areas at the local government to lower levels. Parallel to these fisheries-oriented measures are ecosystem-based management approaches that also consider fisheries management but at the context of

# *Key Characteristics of the First Decade of Systems Biology in the Philippines*

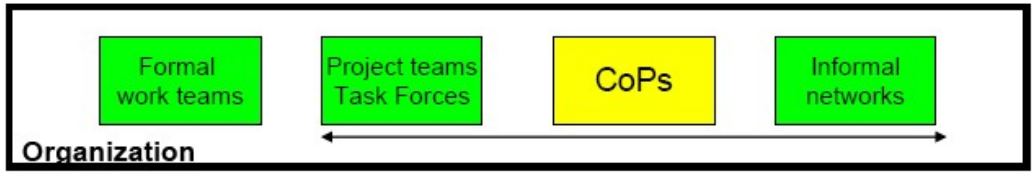
1. *Focus on researchers and students in the UP National University System*
2. *A „Joint Experimeter-Modeler (JEM) Projects in a Community of Practice (CoP)“ approach*
3. *Stronger emphasis on the computational side of Systems Biology*
4. *Major Internet use for collaboration with labs in Europe*
5. *Evolution in 3 phases: 2003-07, 2008-2010, 2011-2013 (start of focus on local collaborations)*

# Research with JEMs and CoPs

### *The Ideal JEM Cycle*

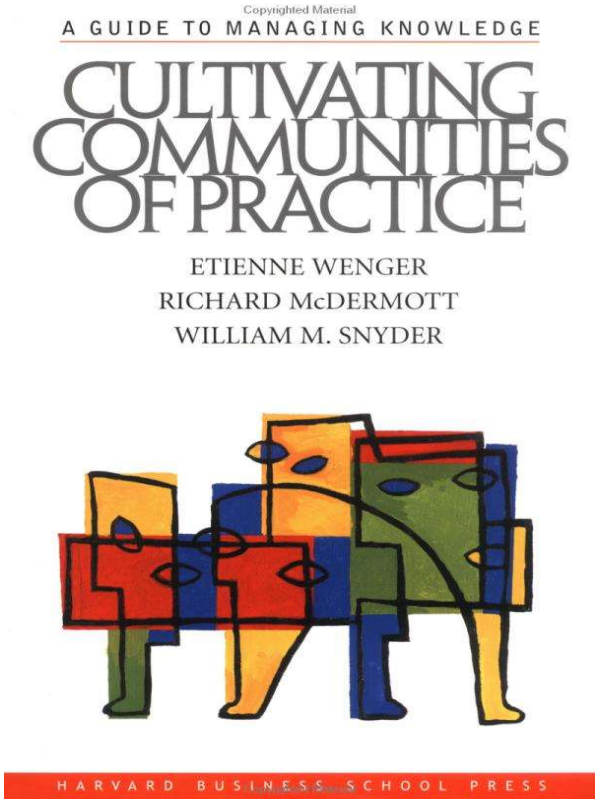



(Kitano, Science 02)




**(F. Nickols, 2003)**

### *Learning from Business*




CoPs are „groups of people in organizations that form to

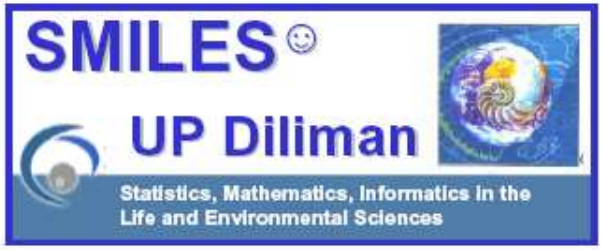
- **share** what they know
- **learn** from one another regarding some aspects of their work
- provide a **social context** for that work

# *Inspiration from CeNS and CSBi*

- *Founded 1998 by 6 physicists as one of the first nanoscience networks worldwide*
- *Minimal LMU funding targets seeding cross-disciplinary cooperation (events, awards,..)*
- *Community has led to many successful joint research proposals, joint teaching/ mentoring, 8 successful spin-offs*
- *Now crosslinks over 100 researchers and 200 PhD/MS students in physics, chemistry, biology, medicine and pharmacy to promote progress in nanoscience and nano-bioscience*
- *Cf: http://www.cens.de/*


- *Initiated mid-2002 by young faculty members from Biology & Bioengineering*
- *CSBi „has been established as a community of practice, built around a shared vision linking science and technology“*
- *Critical forces for integration within CSBi:*
  - *Multi-investigator research collaborations*
  - *A shared Technology Platform*
  - *Joint teaching and supervision of graduate/postdoctoral fellows*
  - *Centrally administered community-building and outreach programs*
- *Now has 80 faculty members from MIT‘s Schools of Science and Engineering, Sloan School of Management and the Whitehead Institute for Biomedical Research*
- *Cf. http://csbi.mit.edu/*

# *SMILES and MBaRC: Filipino CoPs for Systems Biology*





## SMILES ☺

- *Is a multidisciplinary „bottom-up“ **R & E** initiative at UP Diliman focussed on novel computational applications in the Life & Environmental Sciences*
- *began in March 2003 as **MCBI** with Joint Experimenter-Modeller (**JEM**) projects to evolve a **Community of Practice (CoP)***
- *Over 25 projects (till 2011) incl: EUCLIS, theWeP, DOPAKidS, PhilBIS*

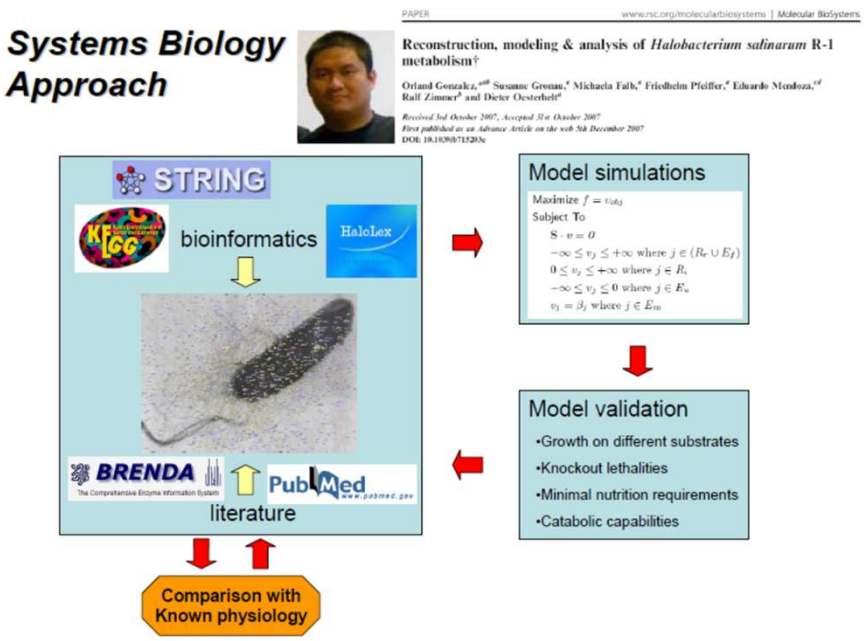
## *MBaRC: Manila Bay Research Corridor*

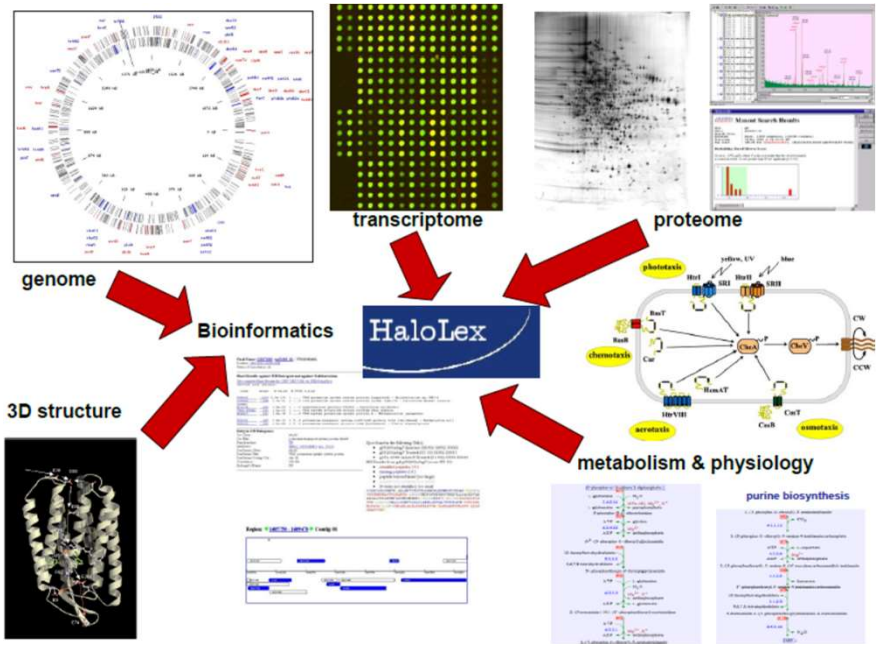
- *An initiative for Computational Life Sciences between:*
  - *DLSU Manila College of Science & College of Computer Studies*
  - *UP Manila College of Arts & Sciences & College of Medicine*
  - *Mapua School of Graduate Studies & Dept of Information Technology*
- *Projects (2008-11) include: MADMan, VirhoLex, CaMBio, PhilSHIFT,…*

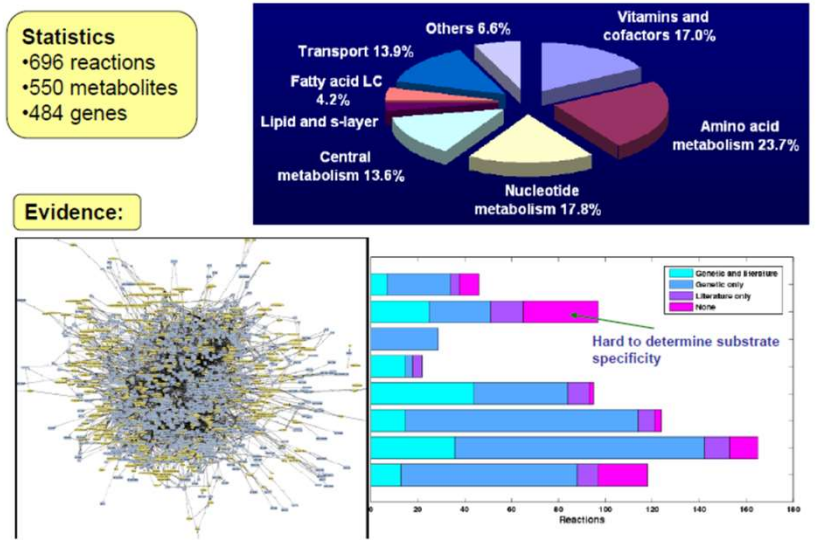
# Project Highlights: Modeling (1)

## Microorganisms

- *Collaboration (2005-2008) with Oesterhelt Lab , MPI Biochemistry, renowned experts on halophilic archaea*
- *Pinoys involved: R. del Rosario, O. Gonzalez, C. Talaue, L. Mansueto*
- *9 joint papers, 2 well cited*



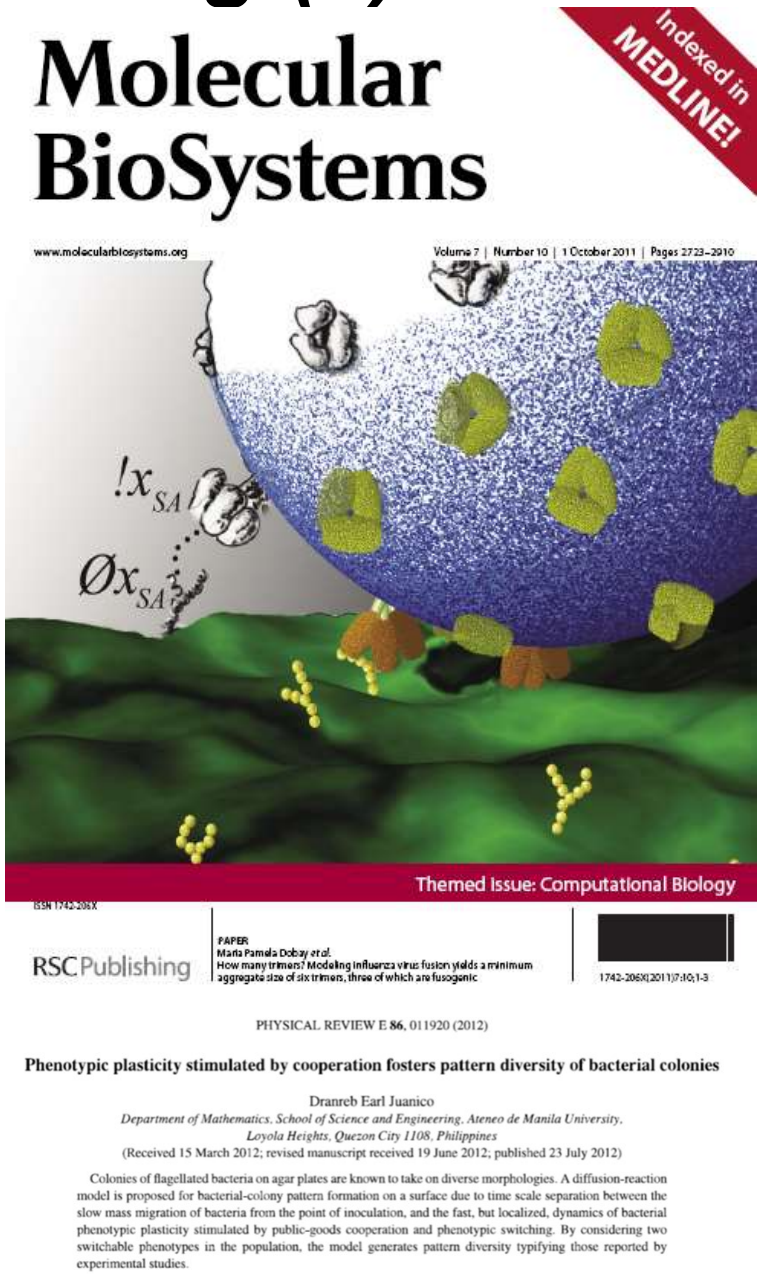



# *Project Highlights: Modeling (2)*

***Microorganisms***

- *Collaboration with Haas Lab (U Edinburgh) on herpesvirus-host interactions*
  - *Postdoc: J. Bantang (MPI Magdeburg fellowship)*
- *Collaboration with Rädler Lab (LMU), van Oijen Lab (Harvard) and Kawasaki Lab (NIID Tokyo) on influenza A membrane fusion*
  - *Part of PhD work of M.P. Dobay (DAAD scholarship)*
- *Collaboration with Frey Lab (LMU) on bacterial colony growth patterns*
  - *Postdoc: E. Juanico (Humboldt fellowship)*



# Project Highlights: Modeling (3)

### *Mammalian cells*

- *Collaboration with Vollmar Lab (LMU) on natural products inducing tumor apoptosis*
- *Support for A. Lao´s PhD (U Rostock) on modeling Alzheimer´s Disease*
- *Collaboration with Tretter Dept (Isar-Amper Hospital) on Computational Neuropsychiatry*

Nat Comput
DOI 10.1007/s11047-009-9153-9

**A discrete Petri net model for cephalostatin-induced apoptosis in leukemic cells**

Eva M. Rodriguez · Anita Rudy · Ricardo C. H. del Rosario · Angelika M. Vollmar · Eduardo R. Mendoza

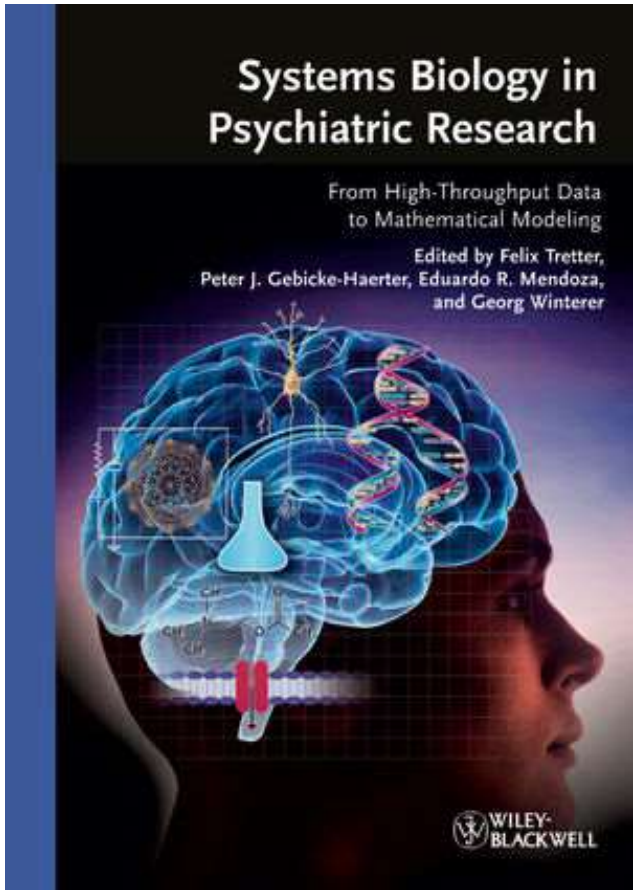
Lao *et al. BMC Systems Biology* 2012, 6:74
http://www.biomedcentral.com/1752-0509/6/74

BMC Systems Biology

RESEARCH ARTICLE Open Access

Multi-compartmental modeling of SORLA's influence on amyloidogenic processing in Alzheimer's disease

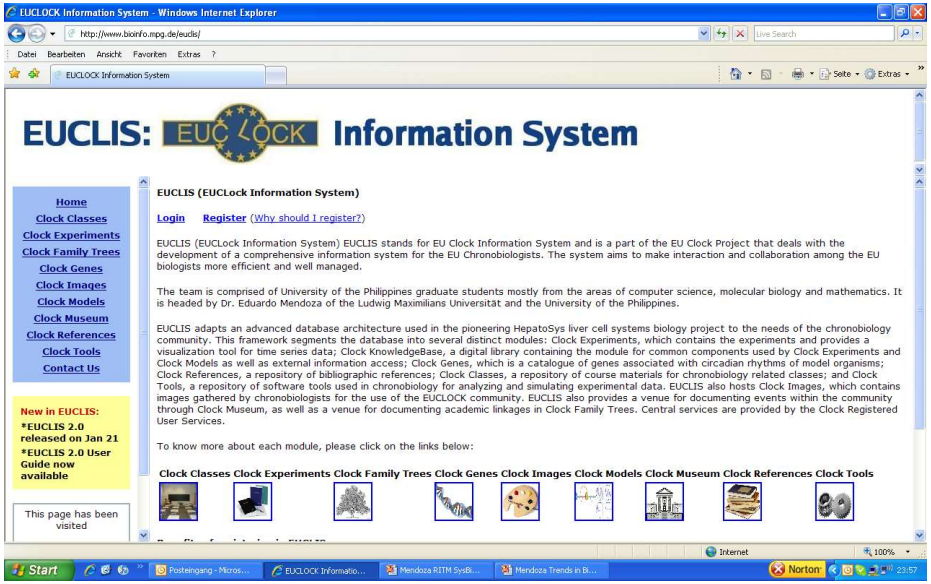
Angelyn Lao[1], Vanessa Schmidt[2†], Yvonne Schmitz[1†], Thomas E Willnow[2*] and Olaf Wolkenhauer[1,3*]



# *Project Highlights: Info-/Knowledgebases*

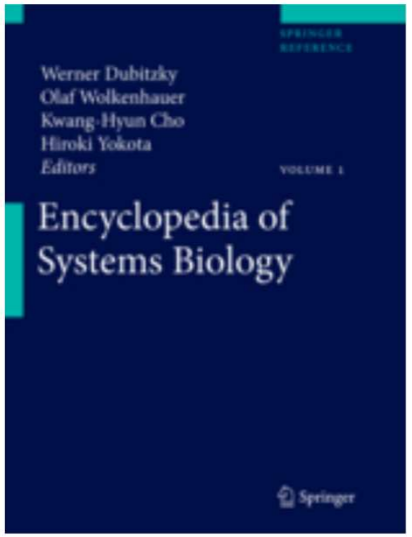
## *EUCLIS*

- ***EUCLOCK** (1/2006-6/2011), an FP6 Integrated Project on the „Entrainment of the circadian clock“, had 30 participants (24 academic, 6 SMEs) and 16 million € funding*
- *As Principal Investigator for the WP „Data Management“, I organized a team at UPD to design and implement EUCLIS (EUCLOCK Information System)*
- *Overall, 9 RA‘s were involved, most completing their MS Math or Comp Science during this time*
- *EUCLIS has now > 1125 registered users; in addition, members of SRBR (Society of Research in Biological Rhythms) can access it directly from SRBR‘s website*



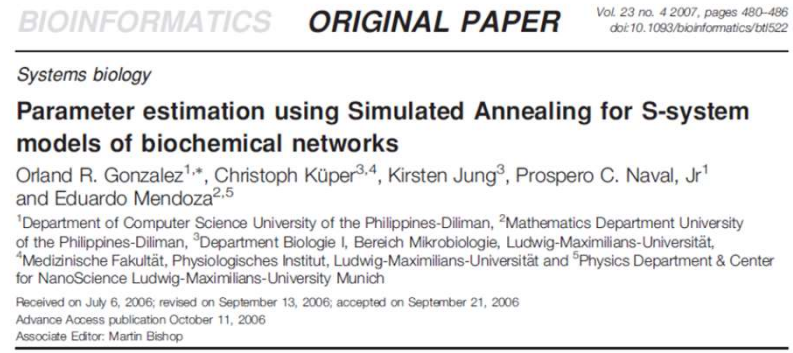

## *Encyclopedia of Systems Biology*

- *„Resources“ Section authored almost exclusively by Filipinos*

# *Project Highlights: Modeling methods*

- *Stochastic parameter estimation methods for models with power law kinetics*
  - *esp. nature-inspired algorithms (PSO, ant colony)*
- *Extensions of stochastic process algebra-based methods*
- *Analysis of mathematical properties of canonical models*



BIOINFORMATICS ORIGINAL PAPER Vol. 23 no. 4 2007, pages 480–486
doi:10.1093/bioinformatics/btl522

*Systems biology*

**Parameter estimation using Simulated Annealing for S-system models of biochemical networks**

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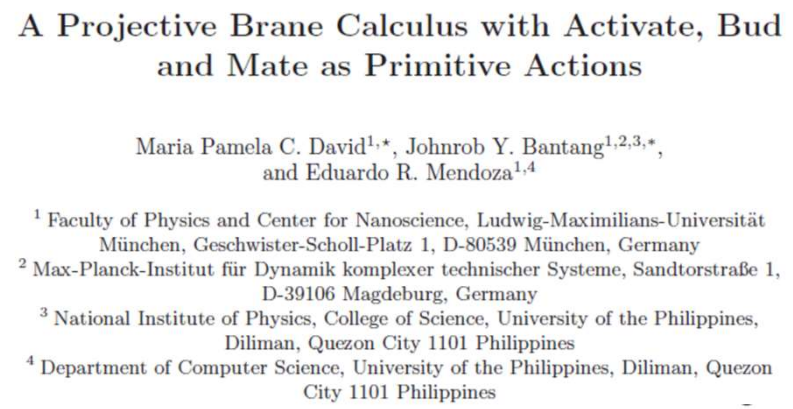
Received on July 6, 2006; revised on September 13, 2006; accepted on September 21, 2006
Advance Access publication October 11, 2006
Associate Editor: Martin Bishop

***136 citations (Google Scholar 3/15/16***



A Projective Brane Calculus with Activate, Bud and Mate as Primitive Actions

Maria Pamela C. David[1,*], Johnrob Y. Bantang[1,2,3,*], and Eduardo R. Mendoza[1,4]

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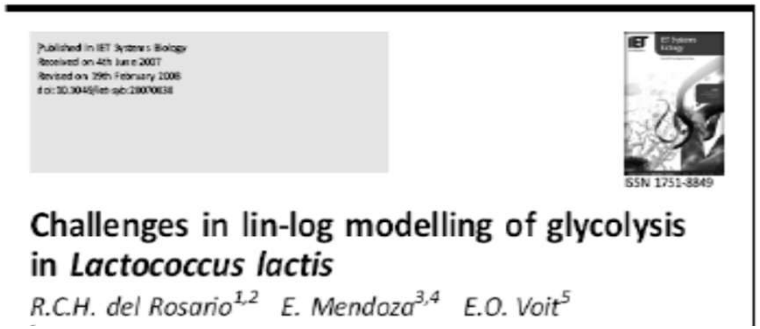


Published in IET Systems Biology
Received on 4th June 2007
Revised on 29th February 2008
doi: 10.1049/iet-syb:20070038

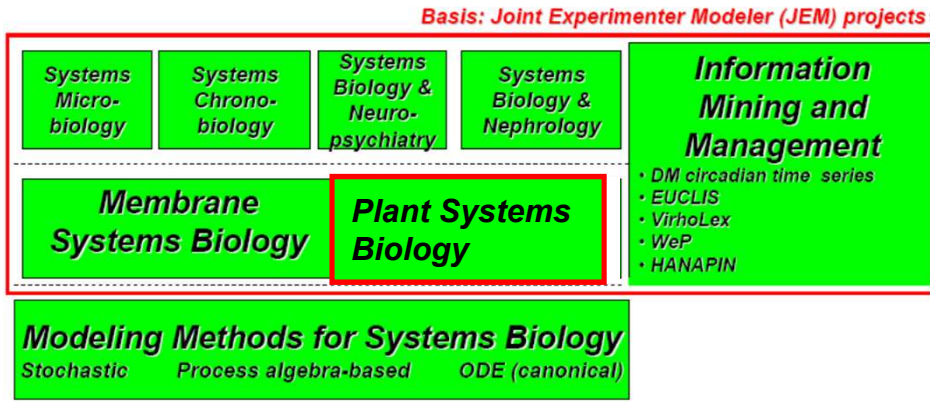
ISSN 1751-8849

**Challenges in lin-log modelling of glycolysis in *Lactococcus lactis***

*R.C.H. del Rosario[1,2] E. Mendoza[3,4] E.O. Voit[5]*

# Results (till Sep 2013)

- *JEMs within the SMILES (Mar 03 – Sep 2010 ), MBaRC (Mar 08 – Sep 2010) and further initiatives*
- *Main results:*
  - *> 35 papers published in international journals ( >30 ISI)*
  - *Graduate studies established at UP Diliman (4 PhDs, 2 PhD cands, > 20 MS, 3 MS cands), UP Los Baños (2 PhD & 2 MS cands), UP Manila (4 MS)*
  - *Collaboration with European labs → 5 Postdoctoral Fellowships, 8 PhD scholarships*
  - *More recently: 2 Phil-funded PhD scholarships*




*Mendoza Group. Munich May 2009*

# *2. The Present: Challenges in a Periof of Transition*

- *2011-12: Start of focus shift to local collaborations*
- *Motivating factors:*
  - *Improved infrastructure (NSC, PGC, ERDT)*
  - *more local support for research (DOST, UP, CHED)*
  - *Less collaboration opportunities after my LMU retirement (Oct 2011)*
- *Further transition aspect: more focus on OMICS data*
- ***Bigger than we thought:* the challenge of finding local experimental partners with quantitative molecular/cellular level data**

# *Example 1: DenCET (Dengue: Climate, Evolution and Transmission)*

- *Collaboration with NIH NIMBB (R. Destura), PAGASA, DOH and National Chung Hsing U (Taiwan)*
- *Phil funding: 15 million pesos (2012- )*
- *Integrated analysis of data on virus evolution, climate and outbreaks from Phil and Taiwan to develop predictive model*
- *PI Modeling: ERM → Joma Escaner (UPD I-Math) → Johnrob Bantang (UPD NIP)*
- *Despite many challenges (incl. political), initial results in papers presented at SPP meeting (Oct 2015)*


## Output

- The proposed ultimate end product is to build a Dengue disease outbreak detection system in the form of a mathematical model, which incorporates all the possible identified factors influencing the occurrence of dengue cases such as:
  - environmental factor (rural or urban, population density), vector (species, migration, behavior)
  - viral metagenomics (type of strain, pathogenicity, genetic profile)
  - Climatic behavioral patterns

Network analysis of Dengue epidemics in the Philippines

Jaime Lorenzo C. Olivares[1*], Raul V. Destura[2] and Johnrob Y. Bantang[1]
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[2] National Institutes of Health, University of the Philippines, Manila
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Investigating the role of quarantine and screening efficiency in dengue epidemics

Pio Gabrielle B. Calderon[1*], Raul V. Destura[2] and Johnrob Y. Bantang[1]
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*Corresponding author: pcalderon@nip.upd.edu.ph

# Example 2:

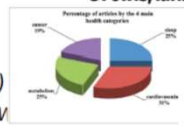
PhilSHIFT

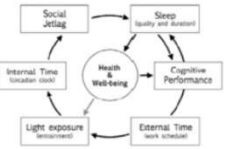
- *Partners: UP Manila (CPH, CM, CAS), UPOU, UPD DCS, LMU, HMS*
- *Funding: UP System (CIDS), DOST (PCHRD)*
- *Inspired by ClockWork (2006-2011)*
- *Cooperation with BPM industry associations (IBPAP, CCAP,…)*
- *Current projects: survey of Filipino chronotype and social jet lag (online/onsite), adaptation of MCTQ-shiftwork questionnaire to phil CC industry*
- *PL: Gayline Manalang Jr. (UPM CPH), projects form part of her PhD work at LMU Center for International Health*

## *PhilSHIFT: A new opportunity for innovation*

- *Shiftwork is a global phenomenon, e.g.*
  - *In highly industrialized countries, 25-30% of work population do shiftwork*
  - *In the Philippines, dramatic increase due to rapid growth in BPO sectors (call centers, etc.)*
- *Epidemiological studies have linked shiftwork to various health risks (esp. cardiovascular, cancer, metabolic, sleep disorder)*
- *Recent research has shov that the disruption of the body's internal timing system (the circadian clock) plays a pivotál role*

Of owls, larks and alarm clocks






## *Goals: take advantage of inter-individual variability of chronotypes to*

- *devise strategies that minimize shiftwork-induced health risks*
- *optimize shiftwork schedules that increase wellbeing, performance and productivity while decreasing health costs*

## *Reducing health risks and improving productivity in a Key Industry*

- *The Call Center (CC) sector is often called a „sunshine industry" due to its*
  - *impressive growth in revenues (2005: $ 1 B to 2013: $10 B); the larger BPO sector reported $15.5 B in 2013, ~ 7% of GDP*
  - *Corresponding employment contribution (2013: 596 K for CC, 900 K for BPO)*
  - *Predicted continued annual growth at 15-17% (for both CC and BPO sectors)*

P6-billion UP-Ayala techno park opens

The New York Times Business Day

A New Capital of Call Centers

REVIEW

**Shift work research in the Philippines: current state and future directions**

Jingky P. Lozano-Kühne[7*], Maria Eliza R. Aguila[1], Gayline F. Manalang, Jr.[2], Richard Bryann Chua[3], Roselyn S. Gabud[5], Eduardo R. Mendoza[4,6]

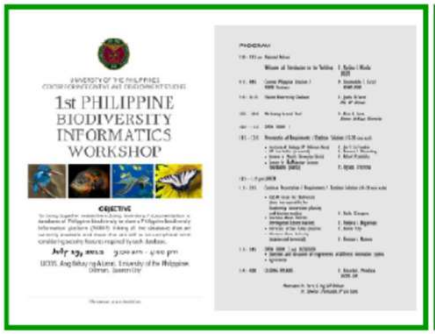


ARTICLE

**An assessment of chronotype and social jetlag among Filipinos**

Roselyn S. Gabud[1,2,8], Gayline F. Manalang Jr.[3,6,8], Richard Bryann L. Chua[1,4,8], Eduardo R. Mendoza[1,2,4,5,8], and Jingky P. Lozano-Kühne*[7,8]

# *Example 3: PhilBIS (Philippine Biodiversity Information System)*



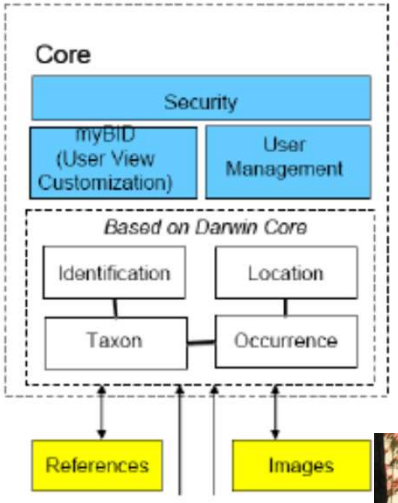

- *Philippine megabiodiversity vs. rare info sharing among Filipino researchers and general scarcity of online info*
- *Collaboration between UPD, UPLB, UPM, DENR, ADNU, U Manchester*
- *Funding: UP System (CIDS) 2013-14 Newton Fund (2015-2017)*
- *Jan 2015: PhilBIDA (PhilBIS Database Application) V1.0 released*
- *Current activity: text-mining assisted curation of dipterocarps in **COPIOUS** project (part of R. Gabud´s PhD research at UPLB)*

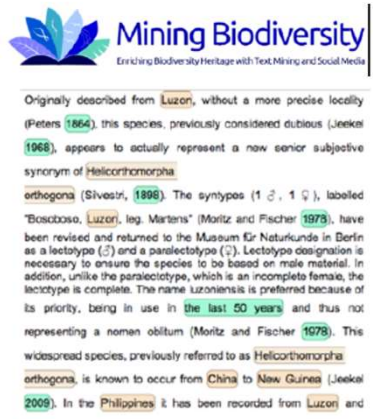
**GBIF: dearth of data on philippine megadiversity**

- *Data about the Philippines*
  - *571 occurrence data sets with 775, 305 records*
  - *no relevant metadata-only data sets*
  - *33 countries contribute data*

*Data from the Philippines*

- *no occurrence data sets*
- *one metadata-only dataset*
- *Philippines publishes data covering no countries*




# *Example 4: Systems genomics of rice salt stress*

- *Collaboration with UPD DCS (H. Adorna) and IRRI (R. Mauleon)*
  - *Major part of J.M. Yap´s PhD thesis (ERDT scholarship)*
- *Main challenge: insufficient amount of ´omics data for initial approach*
- *New method developed and successfully applied*
- *Additional benefit: initial contact with Plant Systems Biology Group (X.G. Zhu) at PICB Shanghai*

ARTICLES

nature genetics

An integrative genomics approach to infer causal associations between gene expression and disease

Eric E Schadt[1], John Lamb[1], Xia Yang[2], Jun Zhu[1], Steve Edwards[1], Debraj GuhaThakurta[1], Solveig K Sieberts[1], Stephanie Monks[3], Marc Reitman[4], Chunsheng Zhang[1], Pek Yee Lum[1], Amy Leonardson[1], Rolf Thieringer[5], Joseph M Metzger[6], Liming Yang[6], John Castle[1], Haoyuan Zhu[1], Shera F Kash[7], Thomas A Drake[8], Alan Sachs[1] & Aldons J Lusis[2]

ARTICLE

**A partial regression coefficient analysis framework to infer candidate genes potentially causal to traits in recombinant inbred lines**

Jan Michael Yap[1]*, Ramil Mauleon[2], Eduardo Mendoza[1,3], and Henry Adorna[1]

Cell

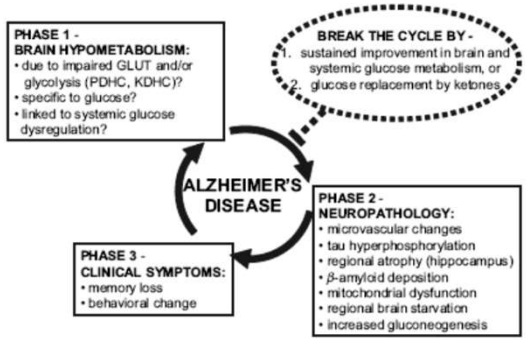
Leading Edge
Review

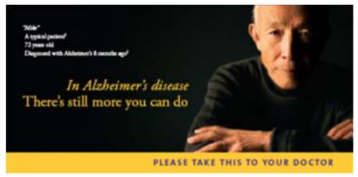
**Meeting the Global Food Demand of the Future by Engineering Crop Photosynthesis and Yield Potential**

Stephen P. Long,[1,2,*] Amy Marshall-Colon,[1] and Xin-Guang Zhu[3,4]
[1]Department of Plant Biology and Institute for Genomic Biology, University of Illinois, Urbana, IL 61801, USA
[2]Department of Crop Sciences, University of Illinois, Urbana, IL 61801, USA
[3]CAS Key Laboratory for Computational Biology, CAS-MPG Partner Institute for Computational Biology, Shanghai 200031, PRC
[4]State Key Laboratory of Hybrid Rice, Changsha, Hunan 410125, PRC
*Correspondence: slong@illinois.edu
http://dx.doi.org/10.1016/j.cell.2015.03.019

# *Example 5: Metabolic aspects of Alzheimer´s Disease (AD)*

- *Collaboration between ADMU Chemistry (F. Dayrit) and UPD I-Math (C. Talaue, C. Arceo) on ketone body metabolism and its possible role in AD*
  - *KeBAP eJournal Club*
  - *Model of KB brain metabolism (S. Mariano MS thesis 2014)*
  - *VCO-AD project (ADMU, DOST ITDI) initiated 2015 (Funding: PhilCOA via PCHRD)*
- *Construction of a model for brain insulin resistance from a T2DM model by A. Lao (DLSU Math)*



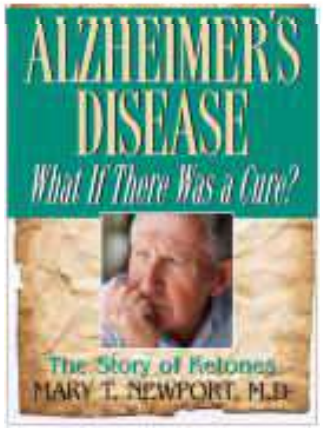



Research article

Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline

Konrad Talbot,[1] Hoau-Yan Wang,[2] Hala Kazi,[1] Li-Ying Han,[1] Kalindi P. Bakshi,[2] Andres Stucky,[2] Robert L. Fuino,[1] Krista R. Kawaguchi,[1] Andrew J. Samoyedny,[1] Robert S. Wilson,[3] Zoe Arvanitakis,[3] Julie A. Schneider,[3] Bryan A. Wolf,[4,5] David A. Bennett,[3] John Q. Trojanowski,[5] and Steven E. Arnold[1]

[1]Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania, USA. [2]Department of Physiology, Pharmacology, and Neuroscience, Sophie Davis School of Biomedical Education, City University of New York Medical School, New York, New York, USA. [3]Rush Alzheimer's Disease Center and Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois, USA. [4]Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA. [5]Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.


**Alzheimer's Researchers Receive NIH Grant to Test Intranasal Insulin Spray**

*By Randi Hernandez, Associate Editor/Online*
**Published Online:** Wednesday, May 16, 2012

***Researchers will receive $7.9 million over the next 5 years to test the effects of intranasal insulin therapy on patients with mild cognitive impairment and mild to moderate Alzheimer's disease.***

Brain Insulin Resistance Marker May Diagnose Alzheimer's

Megan Brooks
November 25, 2014

# *3. The Potential: some short- and mid-term Opportunities*

***A good moment in time to look forward with…***

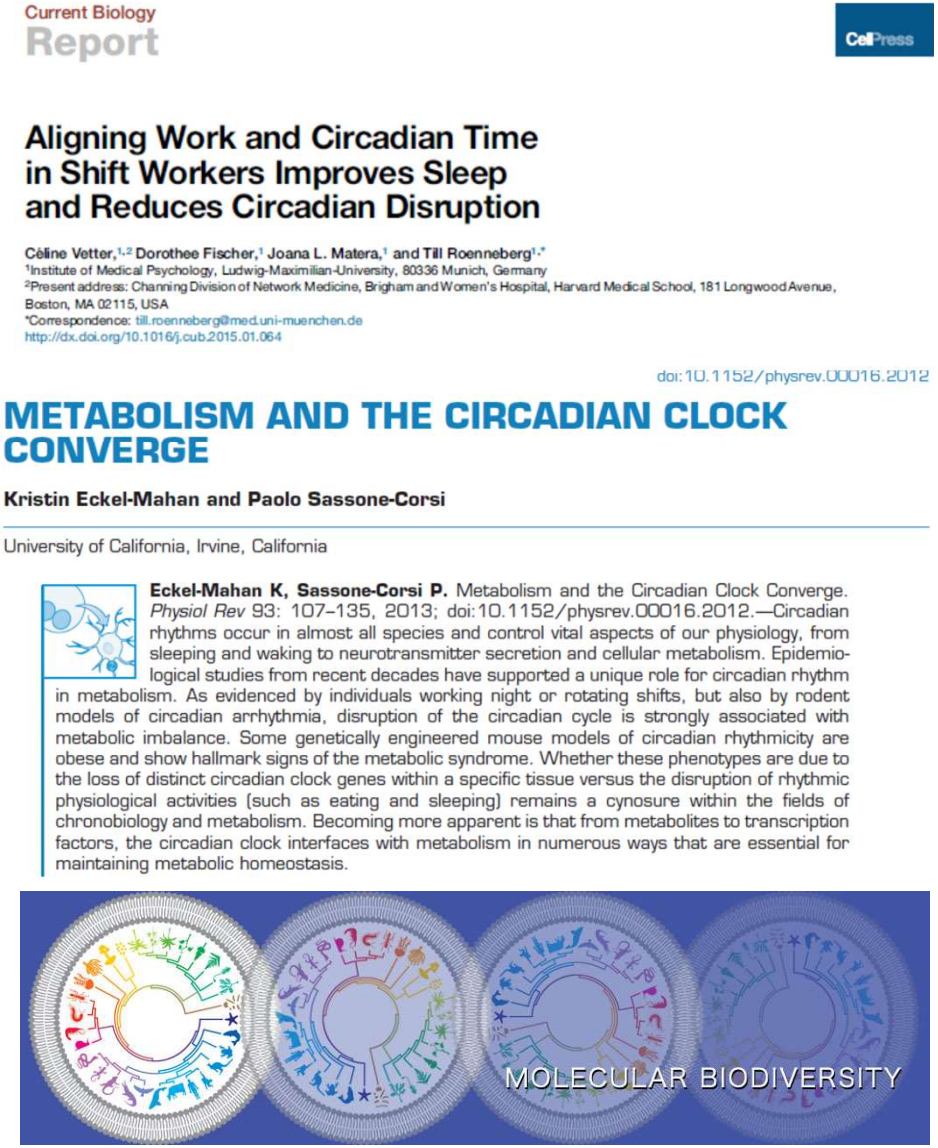
- *a number of **NGCS** (Next Generation Computational Scientists) are active in SysBio-oriented work in the country (A. Lao, JM Yap, J. Tubay, J. Rabajante, D. Indong,…)*
- *an active, global online network (Facebook group) on „Systems Biology and Biomathematics“ initiated by young Pinoy researchers*
- *the PGC under the leadership of B. Aguda poised to accelerate and expand SysBio-oriented initiatives*

# *Short-term SysBio Opportunities*

- ***Systems Biology of virus-host interactions***
  - *Build on previous dengue epidemiological projects (i.e. DenCET) to initiate modeling on molecular/cellular level (e.g. planned PGC workshop,..)*
  - *Expand (mid-term) to a SysBio of virus-host interactions Group (including expatriate experts like P. Dobay,…)*
- ***Systems Biology of Brain Energy Metabolism***
  - *VCO-AD: reboot modeling activities when data becomes available*
  - *Continue construction of brain insulin resistance model*
  - *Mid-Long-term relevance for the Philippines:*
    - *WHO predicts 3 x diabetes cases in Phil by 2030 (Region: 2x)*
    - *growing evidence for strong connections between T2DM and AD (some researchers call AD „type 3 diabetes“)*

# *Mid-term SysBio Opportunities (1)*

- ***PhilSHIFT***
  - *(short-term) will retain occupational health focus (e.g. field studies)*
  - *(mid-term) deepen molecular/ cellular understanding of health issues (e.g. metabolic diseases)*
- ***PhilBIS***
  - *(short term) broaden use of PhilBIDA for research collaboration and online info provision*
  - *(mid-term) extend PhilBIDA to accommodate molecular info and connect to external resources incl. OMICS databases*



Current Biology
Report

CellPress

**Aligning Work and Circadian Time in Shift Workers Improves Sleep and Reduces Circadian Disruption**

Céline Vetter,[1,2] Dorothee Fischer,[1] Joana L. Matera,[1] and Till Roenneberg[1,*]
[1]Institute of Medical Psychology, Ludwig-Maximilian-University, 80336 Munich, Germany
[2]Present address: Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, 181 Longwood Avenue, Boston, MA 02115, USA
*Correspondence: till.roenneberg@med.uni-muenchen.de
http://dx.doi.org/10.1016/j.cub.2015.01.064

doi:10.1152/physrev.00016.2012

**METABOLISM AND THE CIRCADIAN CLOCK CONVERGE**

**Kristin Eckel-Mahan and Paolo Sassone-Corsi**

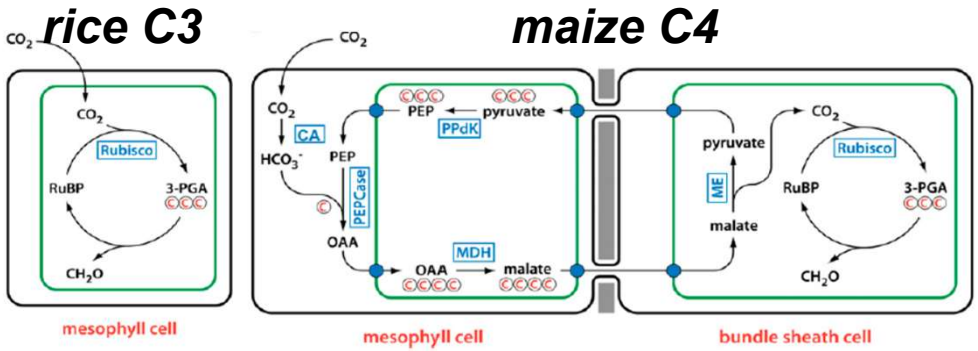
University of California, Irvine, California

**Eckel-Mahan K, Sassone-Corsi P.** Metabolism and the Circadian Clock Converge. *Physiol Rev* 93: 107–135, 2013; doi:10.1152/physrev.00016.2012.—Circadian rhythms occur in almost all species and control vital aspects of our physiology, from sleeping and waking to neurotransmitter secretion and cellular metabolism. Epidemiological studies from recent decades have supported a unique role for circadian rhythm in metabolism. As evidenced by individuals working night or rotating shifts, but also by rodent models of circadian arrhythmia, disruption of the circadian cycle is strongly associated with metabolic imbalance. Some genetically engineered mouse models of circadian rhythmicity are obese and show hallmark signs of the metabolic syndrome. Whether these phenotypes are due to the loss of distinct circadian clock genes within a specific tissue versus the disruption of rhythmic physiological activities (such as eating and sleeping) remains a cynosure within the fields of chronobiology and metabolism. Becoming more apparent is that from metabolites to transcription factors, the circadian clock interfaces with metabolism in numerous ways that are essential for maintaining metabolic homeostasis.

# Mid-term SysBio Opportunities (2)

## Rice Systems Biology

- ***C4 Rice Project*** *(2009- ) addresse potential mid-century food crisis by engineering C4 photosnthesis in rice (~ 40% higher yield)*
  - *Funded mainly by BMGF ($32.2 million to date), Phases I & II (mostly genetics) led by IRRI*
  - *Phase III (Jan 2016 -) led by J. Langdale (Oxford U), more SysBio-oriented*
- *ongoing PhD CS by M. Clariño (UPLB) on leaf venation changes from C3 to C4 (Co-advisor: X.G. Zhu)*
- *(mid-term) prospects*
  - *model „Golden Rice" metabolism*
  - *submit joint proposal to Newton Fund (contact with Oxford & PICB initiated)*
  - *Establish crop-focussed Plant SysBio group*




*Journal of Experimental Botany*, Vol. 65, No. 13, pp. 3327–3339, 2014
doi:10.1093/jxb/eru015

Journal of Experimental Botany

REVIEW PAPER

**Cracking the Kranz enigma with systems biology**

**Jim P. Fouracre, Sayuri Ando and Jane A. Langdale***

Department of Plant Sciences, University of Oxford, South Parks Road, Oxford, OX1 3RB, UK

* To whom correspondence should be addressed. E-mail: jane.langdale@plants.ox.ac.uk

Plant, Cell & Environment

*Plant, Cell and Environment* (2015) doi: 10.1111/pce.12673

Special Issue

**Plants *in silico*: why, why now and what?—an integrative platform for plant systems biology research**

Xin-Guang Zhu[1], Jonathan P. Lynch[2], David S. LeBauer[3], Andrew J. Millar[4], Mark Stitt[5] & Stephen P. Long[6]

PNAS

PERSPECTIVE

**Redesigning photosynthesis to sustainably meet global food and bioenergy demand**

Donald R. Ort[a,b,c,1], Sabeeha S. Merchant[d,e], Jean Alric[f], Alice Barkan[g], Robert E. Blankenship[h,i], Ralph Bock[j], Roberta Croce[k], Maureen R. Hanson[l], Julian M. Hibberd[m], Stephen P. Long[b,c,n], Thomas A. Moore[o,p], James Moroney[q], Krishna K. Niyogi[r,s,t], Martin A. J. Parry[u], Pamela P. Peralta-Yahya[v], Roger C. Prince[w], Kevin E. Redding[o,p], Martin H. Spalding[x], Klaas J. van Wijk[y], Wim F. J. Vermaas[p,z], Susanne von Caemmerer[aa], Andreas P. M. Weber[bb,cc], Todd O. Yeates[d,e], Joshua S. Yuan[dd], and Xin Guang Zhu[ee]

# *Mid-term SysBio Opportunities (3)*

## *Genome-scale metabolic networks of PGC-sequenced organisms*

- *e.g. crops such as abaca, coconut, biotech-relevant microorganisms*
- *Numerous software tools (open access/source) available => feasible for MS work*
- *Prerequisite: annotation of sufficient quality, close collaboration with bio-experts*

Nucleic Acids Research Advance Access published April 6, 2015

*Nucleic Acids Research, 2015* **1**
*doi: 10.1093/nar/gkv294*

**Reconstructing genome-scale metabolic models with *merlin***

**Oscar Dias*, Miguel Rocha, Eugénio C. Ferreira and Isabel Rocha***

Centre of Biological Engineering, University of Minho, Campus de Gualtar, 4710–057 Braga, Portugal

BIOINFORMATICS **ORIGINAL PAPER** *Vol. 28 no. 13 2012, pages 1752–1758*
*doi:10.1093/bioinformatics/bts267*

*Systems biology* Advance Access publication May 4, 2012

**GEMSiRV: a software platform for GEnome-scale metabolic model simulation, reconstruction and visualization**

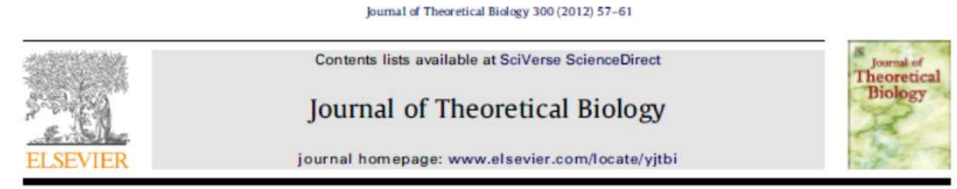
Yu-Chieh Liao[1,*,†], Ming-Hsin Tsai[1,2,†], Feng-Chi Chen[1] and Chao A. Hsiung[1,*]

[1]Division of Biostatistics and Bioinformatics, Institute of Population Health Sciences, National Health Research Institutes, Zhunan 350 and [2]Department of Computer Science, National Tsing Hua University, Hsinchu, Taiwan, R.O.C.

Associate Editor: Trey Ideker

# *Mid-term SysBio Opportunities (4)*

- *Contributions to **Mathematical** Systems Biology*
- ***Qualitative** modeling in Chemical Reaction Network Theory (CRNT) can deliver significant results*
- *Current activities:*
  - *Initial publications on extending beyond mass action kinetics (2015, 2016 under review)*
  - *MCRNKS course offerings at UPD (2014), UPLB (2015), DLSU (2016)*
  - *2 UPD MS students (1 Math, 1 CompSci)*


Journal of Theoretical Biology 300 (2012) 57–61

Contents lists available at SciVerse ScienceDirect

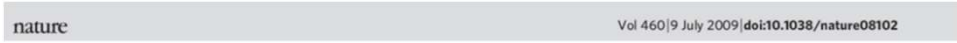
Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

The role of theorem proving in systems biology **(2012)**

Olaf Wolkenhauer [a,b,*], Darryl Shibata [c], Mihajlo D. Mesarović [d]

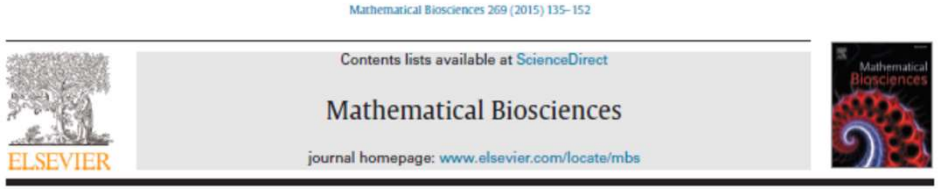
[a] Department of Systems Biology and Bioinformatics, University of Rostock, Rostock, Germany
[b] Stellenbosch Institute for Advanced Study (STIAS), Wallenberg Research Centre at Stellenbosch University, Stellenbosch, South Africa
[c] Department of Pathology, University of Southern California Keck School of Medicine, LA, USA
[d] Complex Systems Biology Center, EECS Department, Case Western Reserve University, Cleveland, USA


nature Vol 460|9 July 2009|doi:10.1038/nature08102

LETTERS

**Unlimited multistability in multisite phosphorylation systems** **(2009)**

Matthew Thomson[1] & Jeremy Gunawardena[2]


Mathematical Biosciences 269 (2015) 135–152

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

Chemical reaction network approaches to Biochemical Systems Theory **(2015)**

Carlene Perpetua P. Arceo [a], Editha C. Jose [b], Alberto Marin-Sanguino [c], Eduardo R. Mendoza [a,b,d,e,*]

[a] Institute of Mathematics, University of the Philippines Diliman, Quezon City 1101, Philippines
[b] Institute of Mathematical Sciences and Physics, University of the Philippines Los Baños, Laguna 4031, Philippines
[c] Division of Systems Biotechnology, Technische Universität München, Munich, Germany

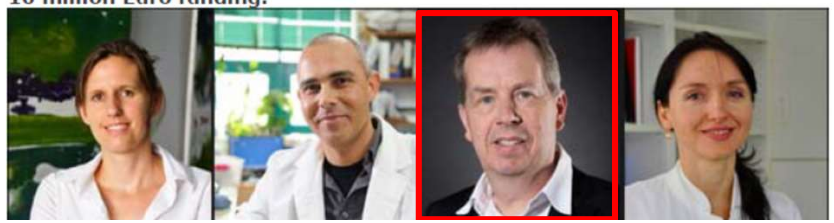
# 2 Very Short-Term Opportunities

- ***Till Roenneberg*** *Visit (Sept 19-28, 2016)*
  - *Renowned chronobiologist*
  - *PhD (LMU 1982), Postdoc (MPI Erling-Andechs,1982-1985), Research Associate (1985-88, Harvard U), 1988 – pres. LMU (Full Professor since 2001)*
  - *2005-11: Coordinator EUCLOCK and ClockWork projects*
  - *Past President, EBRS & WFSC*
- ***Chris Turck*** *Visit (late November 2016)*
  - *Head, Proteomics and Biomarkers Lab, MPI of Psychiatry, Munich*
  - *PhD (Aachen U, 1983), Postdoc (Roche Institute 1983-86), UCSF Dept of Medicine (1986-2002, Full Professor since 2000), 2002 - present, MPI of Psychiatry*


**Four Max Planck Institute scientists receive EU grant funding**

December 04, 2013

Diseases of the brain or nervous system are estimated to lead to worldwide costs of several hundred billion Euro every year. To foster transnational neuroscience research in Europe, the European Commission makes funding available through the ERA-Net NEURON Program. This year, four scientists of the Max Planck Institute of Psychiatry (MPIP) successfully applied for support and will receive a portion of the 10 million Euro funding.



***Thanks for your attention!***

***Questions ?***