Instituto Nacional de Medicina Genómica
MÉXICO

Red de Apoyo a la Investigación

2nd International Summer Symposium on Systems Biology

August 2-4, 2016
INMEGEN
Mexico City

Human SYSTEMS BIOLOGY

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Welcome from Osbaldo Resendis, Conference Chair

The medicine of this century is suffering a transformation. With the advent of high-throughput technologies and computational biology, the opportunity to uncover the genetic mechanisms underlying human diseases is a major aim in the scientific community. Consequently, new conceptual paradigms are emerging in the biomedical and clinical field, for instance the idea of the precision medicine: a medicine for the right patient applied at the right time and the right dose.

This enterprise is a dream that could have in short time important implications in health programs around the world. In parallel, we have been witnesses of some breakthroughs in the genome sciences, such as the availability of NGS and other HT technologies, the genome scale computational modeling of metabolic pathways, the microbiome and its close relationship with diseases, the bioinformatic analysis of massive data and the analysis of expression of single cell, to name a few. Together, these technical and scientific advances are the bases to move toward the uncovering of fundamental principles that will contribute to understand what are the mechanisms that sustain wellness or disease, and how these may emerge in our human organism. This is a great challenge and many obstacles should be overcome. With great pleasure I announce the 2nd International Summer Symposium on Systems Biology (IS3B) which took place in Mexico City, Mexico from August 2nd - 4th 2016, organized by The Human Systems Biology Laboratory (HSBL), RAI-UNAM & INMEGEN. The IS3B is currently the largest symposium on Systems Biology in Mexico and Latin America, and strives to unite leading researchers and students in an informal setting with the aim to present current research in Systems Biology and Systems Medicine. The aims of the meeting were:

- Discuss current research in Systems Biology and its applications for understanding human diseases
- Create an ambiance that enables scientific collaborations, mainly but not exclusively among experimental and theoretical groups

Both purposes are the soul of this event. This report represents the abstracts of the lectures carried out during these three days that embraced topics such as the 100K wellness project in precision medicine, the identification of phenotype of genetic circuits, the modeling of cancer metabolism and the modeling of drug resistance in bacterias. I expect that this symposium will motivate young researchers to make a commitment in this field and move toward the development of the precision medicine through the collaborative effort of various disciplines, an aim that will have strong implications to improve the health population in our country.

Osbaldo Resendis
Human Systems Biology Laboratory (UNAM-INMEGEN)

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General Photograph

Conference Program

Tuesday August 2nd

Oral Session

Wednesday August 3rd

Oral Session

Poster Session

Thursday August 4th

Oral Session

Tuesday August 2nd

Oral session

Aug 2nd
9:00 am

Gene and signaling pathways reveal key processes in the pathogenesis of idiopathic pulmonary fibrosis

Balderas-Martínez Y.I., Engelen K., Pérez-Huacuja-Urista J.M., Castro-Jaimes S., Salgado H., Sonego P., Moretto M., Meysman P., Sánchez-Pérez M., Alquicira-Hernández K., Resendis-Antonio O., Collado-Vides J., Selman M., Pardo A.

Facultad de Ciencias, UNAM; Research and Innovation Center, Fondazione Edmund Mach; Centro de Ciencias Genómicas, UNAM; INMEGEN; Instituto Nacional de Enfermedades Respiratorias Ismael Cosio Villegas

Idiopathic pulmonary fibrosis (IPF) is a chronic disease, progressive, age-related, with unknown etiology. Despite multiple efforts trying to understand the molecular mechanisms involved in the biopathology of this disease, the pathogenesis stills remains as a mystery. Several laboratories have used high-throughput technologies, as microarrays in an attempt to understand the mechanisms, however, as far as we know, there is no meta-analysis that combines these studies and seeks for properties that cannot be seen analyzing individual experiments. In this research, we propose to re-evaluate microarray studies in GEO, in order to find differentially expressed genes, co-expressed genes, and over-represented signalling pathways. Our results contain new genes and pathways that could be important in IPF and may be studied in an experimental model to evaluate their participation in this disease.

Aug 2nd
9:45 am

The 100K Wellness Project: A data-rich longitudinal study for the digital age

Nathan Price

Institute for Systems Biology, Seattle, Washington, US.

Healthcare is becoming more proactive and data-rich than anything before possible - and will increasingly focus on maintaining and enhancing wellness more than just reacting to disease. Lee Hood and I have recently launched a large-scale 100K wellness project that integrates genomics, proteomics, transcriptomics, microbiomes, clinical chemistries and wearable devices of the quantified self to monitor wellness and disease. I present results from our proof-of-concept pilot study in a set of 108 individuals (the Pioneer 100 study) over the past year, showing how the interpretation of this data led to actionable findings for individuals to improve health and reduce risk drivers of disease.

Pan-cancer prediction of proliferation rates and metabolic liabilities

Aug 2nd
10:45 am

Christian Diener

INMEGEN

Cancer is a heterogeneous disease and its genetic and metabolic mechanism may manifest differently in each patient. This creates a demand for studies that can characterize phenotypic traits of cancer on a per-sample basis. Combining two large data sets, the NCI60 cancer cell line panel and the Cancer Genome Atlas, we used a linear interaction model to predict proliferation rates for more than 10.000 cancer samples across 33 different cancers from the Cancer Genome Atlas. The predicted proliferation rates are in good agreement with clinical data and show a strong heterogeneity in proliferative capacity within and across different cancer panels. We also show how the obtained proliferation rates can be incorporated into genome-scale metabolic reconstructions to obtain the metabolic fluxes for more than 2,000 cancer samples that identified specific metabolic liabilities for nine cancer panels.

One day in the life of a one-dimensional developing organism

Aug 2nd
11:30 am

Joel Stavans

Weizmann Institute of Science

Within the last two decades it has become clear that cells having the same genetic information can behave very differently due to inevitable stochastic fluctuations in gene expression, known as noise. Noise can be advantageous in certain contexts but detrimental in others. How do cells in multicellular organisms achieve high precision in their developmental fate in the presence of noise, in order to reap the benefits of division of labor? We address this fundamental question from a Systems Biology perspective with Anabaena cyanobacterial filaments, one of the earliest examples of multicellular organisms in Nature. These filaments form one-dimensional, nearly-regular patterns of cells of two types, when subjected to nitrogen deprivation: some cells carry out nitrogen fixation whereas others fix carbon through photosynthesis. The developmental program uses non-linear processes including activation, inhibition, and transport to create spatial and temporal patterns of gene expression that we can follow in real time at the level of individual cells. This allows us to measure spatial and temporal correlation functions, in both wild type and in mutant backgrounds in which these non-linear processes are abrogated. The results of our statistical analysis illuminate the fundamental role that positive feedback, lateral inhibition and cell-cell communication play in the developmental program, and establish the spatial extent to which gene expression is correlated along filaments.

Aug 2nd
2:00 pm

Sewage captures the daily pulse of a residential neighborhood

Mariana Matus

Massachusetts Institute of Technology

Sewage is an untapped source of biochemical information that can be mined to improve public health, for example by tracking the emergence and spread of infectious diseases or antibiotic resistance genes. One of the outstanding challenges in enabling this such system is to robustly quantify biomarker levels and translate them into population-level metrics. A key step is understanding the underlying level of variation in sewage biomarkers and how this is affected by fluctuations in water usage, the number of contributing individuals, dilution and degradation of biomarkers. Here we report the 24-hour dynamics of bacterial and chemical profiles generated from samples collected at a single manhole representing a small residential neighborhood, and we show that sewage robustly captures daily human activity. Our results indicate that there is a clear day-night difference in the bacterial and metabolite profiles which mirror the water usage pattern in the neighborhood. We define core urinary and fecal signals and show that urinary metabolites are robustly detected throughout the day while fecal metabolites peak around meal times. We describe new methods to normalize observed data by decomposing the signals into urinary and fecal components and by estimating the number of contributing individuals. We apply those correction methods to diet and medication signals to identify meaningful changes. We provide a proof of concept that data captured in sewage reflects human activity in the sampled population and present new metrics and methods to distinguish community-level changes in biomarker levels from random fluctuations in the sewer, thereby enabling future comparisons across communities.

Key Words: *Sewage, Microbiome, Metabolomics, Public Health*

Aug 2nd
2:30 pm

The Systems Biology of Virulence and Resistance: from Single-Cells to Microbial Communities

Rafael Peña-Miller

Centro de Ciencias Genómicas, UNAM

Conventional wisdom states that members of an isogenic community of bacteria living in a homogeneous environment must be identical. For decades, this assumption has sustained the idea that metabolic and genetic properties of individual cells can be inferred from estimates of a distribution of attributes measured in bacterial populations. But recent advances in single-cell technologies have shown that even clonal populations in uniform environments can present a heterogeneous population structure with complex interactions between individuals, a property known as phenotypic heterogeneity. In this talk we will argue that phenotypic noise is not only an unavoidable consequence of the inherent stochasticity of the system, but a potentially evolutionary optimal strategy that can provide functional benefits to bacterial communities. In particular, we will show how non-genetic individuality allows the implementation of cooperative strategies that enable rapid adaptation to hostile and unpredictable environments (e.g. antibiotic therapy) and to perform complex tasks (e.g. host colonization). To achieve this goal, we will use an interdisciplinary approach that combines mechanistic mathematical models with fluorescence microscopy and single-cell microfluidic experiments in order to quantify, with high temporal resolution, gene expression dynamics and morphological properties of individual cells. We will then integrate the obtained metabolic and genetic information into a population-genetics framework with the aim of predicting how cell-to-cell variability can drive ecological and evolutionary processes at a population-level.

Extracellular Small RNAs During Parasite-Host Communication

Aug 2nd
4:00 pm

Ovando-Vazquez C[1], Chow F[2], Koutsovoulos G[2], Maity T[3], Blaxter M[2], Claycomb J[3], Buck AH[2],
Abreu-Goodger C[1]

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[2]Centre for Immunity, Infection & Evolution, University of Edinburgh, UK
[3]Department of Molecular Genetics, University of Toronto, Canada

The discovery of stable small RNAs moving between organisms, suggests the existence of RNA-based communication, with implications for ecology, agriculture and disease. We have previously reported the presence of exosomes with small RNAs and a worm-specific Argonaute in the secretory products of the parasitic nematode Heligmosomoides polygyrus. We are now further characterizing the molecular content of these exosomes, and particularly want to understand the function of the different types of small RNAs during infection. We performed high-throughput sequencing of small RNA libraries from the exosome and supernatant of H. polygyrus secretory products. To aid their characterization, we also used long single-molecule sequencing (PacBio) to improve the genome assembly and annotation of H. polygyrus. This allowed us to determine the genomic locations of the secreted small RNAs. Certain classes of RNAs are enriched in exosomes, including Principal and full-length yRNAs, 22G siRNAs, microRNAs, and specific fragments from tRNAs and rRNAs. Particularly interesting are 22G siRNAs, produced by RNA-dependent RNA polymerases, suggesting that a complex RNA-interference machinery is involved in producing the exosome content. These results will help us understand the functions of exosomes and their cargo during parasitism, and highlight a versatile role for RNA during interactions between organisms.

Funding: This project is supported by an HFSP grant (RGY0069).

Key Words: *small RNA, parasitism, next-generation sequencing, bioinformatics*

Wednesday August 3rd

Oral session

Aug 3rd
9:00 am

An Information Algorithmic Calculus for Reprogramming Biological Systems

Hector Zenil, Narsis A. Kiani and Jesper Tegner

Karolinska Institute and Oxford University

Techniques from graph theory, statistics and entropy have been adapted and often successfully used in different disciplines for characterizing complex data in the language of networks. Zenil will explain how a novel algorithmic calculus can be exploited to reprogram systems, in particular genetic regulatory networks, showing that Shannon's entropy, Kolmogorov-Chaitin's complexity and Solomonoff-Levin's algorithmic probability can quantify different properties of static and evolving (labeled and unlabeled) graphs.

Aug 3rd
9:30 am

Systems Biology: A Phenotype-Centric Approach

Michael A. Savageau

Departments of Microbiology & Molecular Genetics and Biomedical Engineering, University of California

Although we now have a generic concept of 'genotype' provided by the detailed DNA sequence of an organism, there is no corresponding generic concept of 'phenotype'. Without a generic concept of phenotype there can be no rigorous framework for a deep understanding of the complex biochemical systems that link genotype and environment to phenotype. I will contrast the traditional 'parameter-centric' modeling strategy with a new 'phenotype-centric' modeling strategy that inverts many of the key steps in the traditional approach. This new strategy provides a generic definition of phenotype that allows for the automatic enumeration of the phenotypic repertoire based only of the 'architectural' features of the system and independent of its parameter values. It also provides automatically at least one set of parameter values for the realization of each qualitatively distinct phenotype. In this way it addresses the difficult problem of parameter estimation in complex nonlinear systems by providing good start values that can then be refined by any number of conventional techniques. With this phenotype-centric strategy the qualitatively distinct phenotypes of a complex system can be rigorously defined and counted, their fitness analyzed and compared, their global tolerances measured, and their biological design principles revealed. The genotypically-determined parameters, environmentally-determined variables and qualitatively distinct phenotypes are integrated into a system design space that facilitates a more intuitive graphical interpretation. The boundaries between phenotypes in this design space are not assigned subjectively but rather are rigorously defined by the system itself. Thus, they provide an objective scale that distinguishes small from large mutant effects and thereby a resolution of the apparent robustness/evolvability paradox. A few simple applications will be used to illustrate how this approach elucidates the relationship between genotype, environment, and phenotype of biochemical systems. This approach provides quantitative understanding of evolution for a number of natural systems and a global perspective on the phenotypic repertoire that facilitates the directed evolution of synthetic gene circuits.

Key Words: *Design Space, Modeling Strategies, Phenotypic Repertoire, Design Principles*

Metabolic Mechanisms in Cancer

Aug 3rd
10:30 am

Osbaldo Resendis

INMEGEN-RAI-UNAM

Systems Biology is an emergent science whose main objective is to understand and predict the phenotype of a microorganism through the parallel analysis of high throughput data and computational modeling. This systemic, integrative and quantitative description is a new paradigm in genome sciences that contribute to understand the metabolic profile supporting the phenotype in a variety of organism, ranging from the bacteria to the study of metabolic alterations in human diseases. Given the multi-factorial nature of cancer, uncovering its metabolic alterations and evaluating their implications is a major challenge in biomedical sciences that will help in the optimal design of personalized treatments. The advance of high-throughput technologies opens an invaluable opportunity to monitor the activity at diverse biological levels and elucidate how cancer originates, evolves and responds under drug treatments. To this end, researchers are confronted with two fundamental questions: how to interpret high-throughput data and how this information can contribute to the development of personalized treatment in patients. A variety of schemes in systems biology have been suggested to characterize the phenotype states associated with cancer by utilizing computational modeling and high-throughput data. These theoretical schemes are distinguished by the level of complexity of the biological mechanisms that they represent and by the computational approaches used to simulate them. Notably, these theoretical approaches in combination with genome scale metabolic reconstructions have provided a proper framework to explore some distinctive metabolic mechanisms observed in cancer cells, such as the Warburg effect. In this talk I will present some formalisms that can serve as a platform to: 1) integrate and interpret high-throughput data; 2) generate biological hypothesis about their metabolic activity; and 3) design experiments to assess the genotype-phenotype relationship in cancer studies. Given the overwhelming complexity in cancer, multidisciplinary approaches are required to construct the bases of precision medicine, whose development remains as a fundamental task in the medicine of this century.

Metabolic inflammation effects over the gliotransmitters release in mature astrocytes: a network-based approach

Aug 3rd
11:30 am

Daniel Osorio[1,2,3]; Janneth Gonzalez[2]; Andrés Pinzon[3]

[1]Departamento de Ingeniería de Sistemas e Industrial, Facultad de Ingeniería, Universidad Nacional de Colombia
[2]Grupo de Investigación en Bioquímica Experimental y Computacional, Facultad de Ciencias, Pontificia Universidad Javeriana - Bogotá
[3]Grupo de Investigación en Bioinformática y Biología de Sistemas, Instituto de Genética, Universidad Nacional de Colombia

Astrocytes have a central role in keeping brain metabolism. The Neuron-Astrocyte cross-talk is modulated by the release/uptake of several gliotransmitters (GTs). Astrocytes have shown be high sensitive to inflammatory mediators derived from overnutrition (ON) and obesity. In order to propose a mechanism of the meta-inflammation effects over the GTs release in astrocytes we built and modeled a tissue-specific metabolic reconstruction for healthy mature astrocytes; we also simulated a meta-inflammation scenario caused by free fatty acid increase; and compared release rates of ATP, Adenosine, Lactate, Gln, D-serine and GSH between healthy and inflamed scenarios. The model was constructed based in RNA-seq GSE73721 dataset using RECON2 as reference reconstruction. All simulations were carried out through 'sybil' package. Inflamed scenario was modeled increasing the palmitic acid uptake to 0.1 mmol/gDW*hr constant rate based on a FBA robustness analysis results. Each GT release rate was evaluated using a specific objective function together with the human generic biomass function. We found that our model replicates the Lactate release rate previously reported. In all GTs

not associated with energy maintenance, ON affects in a negative way the release rate. Release of D-serine is independent of other GT release and is only measurable under their specific stimuli, while release of Gln, GSH and ATP are very related between them, and are sensible in different quantities to ON scenario.

Aug 3rd
12:00 am

Paralogous Diversification: Possible Repercussion on Metabolic Fluxes

Alicia González[1]; Ximena Martínez de la Escalera Fanjul[1]; James González[1]; Lina Riego-Ruiz[2]

[1]Departamento de Bioquímica y Biología Estructural, Instituto de Fisiología Celular, Universidad Nacional Autónoma de México, Mexico City, México
[2]División de Biología Molecular, IPICYT, San Luis Potosí, México

Our group has studied the functional diversification of four paralogous pairs, whose products are involved in amino acid metabolism: GDH1/GDH3, LYS20/LYS21, BAT1/BAT2, and LEU4/LEU9. Functional diversification has affected transcriptional regulation of the paralogous pairs, and GDH1/3, LYS20/21, and LEU4/9 kinetic behavior of the encoded enzymes has also diverged. These three pairs of paralogous enzymes, which are located in the same sub-cellular compartment, can interact forming homo or hetero-oligomeric isoforms. NADP-glutamate dehydrogenase, homocitrate synthese, branched chain aminotransferase and α-isopropylmalate synthase are respectively involved in glutamate, lysine and leucine biosynthesis and thus consume α-ketoglutarate (α-KG), AcCoA and pyruvate. The capacity of these enzymes is regulated by their inherent rate of substrate utilization and by product-dependent feedback inhibition. During fermentative/respiratory growth, amino acid biosynthesis would be selectively afforded by the isozymes, which use α-ketoacids at a best fitted rate. Accordingly, the existence of multiple isoforms, including homo and hetero-oligomeric derivatives, would provide the pacemaker mechanism that assures optimum amino acid biosynthesis in either fermentative or respiratory conditions without compromising the energy-yielding metabolism.

Aug 3rd
14:00 pm

Prediction of multi-dimensional drug dose-responses based on measurements of drug pairs

Anat Zimmer*, Itay Katzir*, Erez Dekel, Avi Mayo, Uri Alon

Weizmann institute

Finding potent multi-drug combinations against cancer and bacterial infections is a pressing therapeutic challenge; however, screening all combinations is difficult because the number of experiments grows exponentially with the number of drugs and doses. To address this, we present a mathematical model which predicts the effects of three or more antibiotics or anti-cancer drugs at all doses based only on measurements of drug pairs at a few doses, without need for mechanistic information. The model provides accurate predictions on previous data for antibiotic combinations, and on experiments presented here on the response matrix of three cancer drugs at eight doses per drug. This approach opens a way to search for effective multi-drug combinations using a small number of experiments.

MicroRNAs: Principles of Target Recognition and Developmental Roles

Aug 3rd
14:30 am

Vikram Agarwal

University of Washington

MicroRNAs (miRNAs) are 21–24 nt non-coding RNAs that mediate the degradation of target mRNAs. The genomes of vertebrate organisms encode hundreds of miRNAs, each of which may regulate hundreds of mRNA targets. The recognition of a miRNA target is guided largely by perfect base pairing interactions between nucleotides 2–7 from the 5' end of the miRNA and complementary motifs embedded in the 3' UTRs of the target mRNAs. In this study, I evaluate the putative function of "non-canonical" sites that defy these rules, and define contextual features that discriminate effective target sites from ineffective ones. I ultimately build a quantitative model which out-performs existing computational models and experimental approaches in target identification. Using this model, we overhauled our public database for vertebrate miRNA target prediction (TargetScan7.0, http://targetscan.org). I demonstrate the benefit of using such predictions to elucidate the in vivo targeting network of miR-196, a deeply conserved vertebrate miRNA. Our findings support a role for miR-196 in the spatial patterning of the vertebrate axial skeleton during early development.

Key Words: *MicroRNA target prediction, Post-transcriptional gene regulation*

Contextual repositioning of drugs for breast cancer by using an integrated network platform

Aug 3rd
15:30 pm

Aldo Segura-Cabrera[1], Navneet Singh[2], Marco A. Velasco Velázquez[4], Kakajan Komurov[2,3]

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[2]Division of Experimental Hematology and Cancer Biology
[3]Division of Biomedical Informatics, Cincinnati Children's Hospital Medical Center, Cincinnati OH
[4]Facultad de Medicina, Universidad Nacional Autónoma de México (UNAM)

Repositioning of drugs to novel disease indications has a promise of faster clinical translation. However, identifying new pathological contexts for known drugs is not trivial. We have developed an integrated network framework that combines functional molecular interactions with known drug-target pairings to use as a platform for contextual repositioning of drugs. We show that a random walk-based integration of molecular data with this network platform can help to reposition known drug-target or pathway pairings to novel biological contexts. For example, a data-biased random walk-based analysis of our network using genome-wide shRNA screens of lethality across cell lines can accurately identify known drug-context pairings (e.g. lapatinib – HER2+ breast cancers), and identify novel highly potent pairings for HER2+ and triple-negative breast cancer cells, several of which we also verified experimentally. In addition, we show that our approach can be used to design more potent combinatorial strategies based on polypharmacology patterns of drugs. As another important utility of our approach, we also showcase the use of this platform in the analyses of large cell-based compound screens to simultaneously prioritize compounds, and identify their most important target pathways and mechanisms of action in the cell. The integrated network and the approach are integrated into the NetWalker suite for functional genomics.

Poster session

Aug 3rd
4:00 pm

Integrating transcriptomic and metabolomic to understand hepatocellular carcinoma in a rat model

Claudia Erika Hernandez-Patiño[1,2]; Christian Diener [1];Julia Esperanza Torres Mena [4];Julio Perez Carreón[4];Osbaldo Resendis-Antonio[1,3]

[1]Genómica Computacional,Instituto Nacional de Medicina Genomica, Mexico
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[3]Red de Apoyo a la Investigación
[4]Laboratorio Bioquímica de Enfermedades Crónicas, Insitituto Nacional de Medicina Genómica

Hepatocellular carcinoma (HCC) is now the third leading cause of cancer deaths worldwide. Despite this, knowledge about the metabolic states of this disease is limited. Using a rat model that recreates some of the most important characteristics of HCC, including cirrhosis, we aim to understand its metabolic state when compared with healthy liver. We have seen important changes in oxidative stress metabolism in both transcriptome and metabolome. Also the metabolomic data points to changes in pathways like amino acids, glycolysis and TCA. Variation in the data also seems to suggest tumor cells change their metabolism to be more specialised.

Aug 3rd
4:00 pm

Global analysis of the cervical cancer metabolism

Muñoz-González F[1], Valverde M[2], García-Carrancá A[3], Resendis-Antonio O[1]

[1]Instituto Nacional de Medicina Genomica (INMEGEN)
[2]Instituto de Investigaciónes Biomédicas, UNAM
[3]Instituto Nacional de Cancerologia (INCAN)

During the oncogenesis of cervical cancer, with the human as the etiologic factor, several changes including metabolic disorders are generated, which are considered a hallmark of cancer. Using the data available in public databases of transcriptomics and metabolomics we create a method to study and understand the differences between normal biopsies, cancer biopsies, normal and cancer cell lines.

Community Structure in transcriptional networks of breast cancer molecular subtypes

Aug 3rd
4:00 pm

Sergio Alcalá-Corona, Guillermo de Anda-Jáuregui, Jesús Espinal-Enríquez, Enrique Hernández-Lemus

INMEGEN

Breast cancer is a heterogeneous disease, with many clinical manifestations; such is the case of the well known molecular subtypes: luminal A, luminal B, basal and HER2-enriched. Heterogeneity can also be found in transcriptional networks. Particularly, different networks may exhibit different modular structures - also known as communities. These structures may be related to known biological processes and functions. Community structures in transcriptional networks may be seen as possible regulatory structures, manifestations of a tight control in biological processes.

A genome-scale metabolic model of the compatible interaction between *Solanum tuberosum* and *Phytophthora infestans*

Aug 3rd
4:00 pm

Botero-Orozco K[1,2], Pinzón A[1], and Restrepo S[3]

[1]Universidad Nacional de Colombia
[2]Centro de Bioinformática y Biología Computacional de Colombia
[3]Universidad de los Andes

In order to predict the molecular mechanisms of Solanum tuberosum disease called Late Blight, caused by the pathogen *Phytophthora infestans*, we developed a genome scale metabolic model of potato that includes 2055 reactions, 1970 metabolites and 1117 metabolic functions, coupled to additional constrains from microarray data. Flux balance analysis interrogation of the model, showed that the metabolic flux of reactions involved in carbon fixation pathway was altered during infection. We report the first metabolic reconstruction of a specie of the Solanaceae family and computational model of late blight of potato. We suggest that compatible interaction between *P. infestans* and *S. tuberosum* affects photosynthetic activity of the plant.

Biomarker identification of cancer from systems biology perspective

Aug 3rd
4:00 pm

VCSR Chittepu, Poonam Kalhotra, Jaramillo-Flores Maria Eugenia

IPN - Escuela Nacional de Ciencias Biológicas

Identification of bio-markers from systems biology is emerging perspective, and it will help to integrate all technologies applied to cancer across different organs. Chemotherapy treatment suffers patients from metabolic perspective. It is good idea to understand effect of cancer from sytems biological perspective. In our study, FDA approved drugs for breast drugs were collectedusing public databases like pubchem, KEGG, and others were used to collect information about gene expression. we tried to build a QSAR model to connect chemical structure, and genes expressed. Identified model can be used to design new structures and QSAR model can predict effect on genes.

The Ergosome? A multi-protein complex candidate for drug discovery in Leishmania mexicana.

Aug 3rd
4:00 pm

Alpizar-Sosa EA[1]; Gray J[1]; Burchmore R[1]; González M[2]; Gutiérrez CEM[2]; Barrett M[1]

[1]University of Glasgow. Wellcome Trust Centre For Molecular Parasitology
[2]Universidad Autonoma Metropolitana Xochimilco. CBS.

Leishmaniasis is a neglected disease with increasing prevalence in Mexico. No satisfactory treatment is available. The interactome of the biosynthetic pathway of sterols in this parasite was analyzed to identify known protein-protein interactions (PPIs) between enzymes of the pathway. Structural differences were identified between the network reported in the STRING database and other approaches described previously. STRING database was notified for updating their content, this will impact drug discovery and improve the use of orphan drugs for the treatment of Leishmaniasis. Four enzymes were selected for expression in heterologous systems and proteomic and metabolomic analysis to determine PPIs as drug target in Leishmania.

Predictive logical modelling of TLR5 and TCR cooperation for CD4 T cell activation.

Aug 3rd
4:00 pm

Otoniel Rodríguez-Jorge[1]; Linda Aimara Kempis-Calanis[1]; Darely Yaraceth Gutiérrez-Reyna[1]; Oscar Ramírez-Pliego[1]; Wassim Abou-Jaoudé[2]; Morgane Thomas-Chollier[2]; Denis Thieffry[2]; Angélica Santana[1]

[1]Centro de Investigación en Dinámica Celular (CIDC). Instituto de Investigación en Ciencias Básicas y Aplicadas. Universidad Autónoma del Estado de Morelos, México; [2]Institut de Biologie de L'Ecole Normale Supérieure (IBENS - CNRS UMR 8197 - INSERM U 1024), France.

Flagellin provides additional signals to those of the T cell receptor (TCR) for T cell activation. We modeled the cross-talk between the flagellin receptor (Toll-like receptor 5 (TLR5)) and TCR signaling pathways during CD4 T cell activation. We constructed logical models for both pathways, using literature and high-throughput data, and validated them experimentally. We reduced and merged these models and analyzed the effect of perturbations (knock outs) in their dynamical behavior. We stimulated naïve CD4 T cells through the TCR +/- flagellin, measured pIKK$\alpha\beta$, pc-JUN and pCREB by flow cytometry, and used this data to fine-tune our merged model. Our model provides novel insights into the effects of flagelin signals on CD4 T cell activation.

Common Connection Pattern: A new method for the identification of common sub-network connections in large biological networks

Aug 3rd
4:00 pm

Juan David Henao. BSc.[1,2]; Andrés M. Pinzón V. Ph.D [1,3]

[1]Bioinformatics and Systems Biology Group, National University of Colombia, Bogota, Colombia
[2]Masters Student
[3]Principal Investigator.

Common Connection Pattern (CCP) is a new method we developed to find common sub-network connection architectures between large biological networks. We applied it to the finding of CCPs between co-expression networks (obtained from all data in GEO, FDR <0,2; p-value >0,05 kolmogorov smirnov test) and protein

interaction data (from filtered data using STRING database) for three neurodegenerative diseases: Alzheimer (A), Parkinson (P) and Multiple sclerosis (MS). We found 4 CCPs between A and P and 13 between MS and P. These CCPs can be seen as common molecular mechanisms of disease between networks under study and better represent relationships between biological networks than the solely description of common gene sets between diseases.

Biomarker identification for diabetes using chemical gene pathways.

Aug 3rd
4:00 pm

Poonam Kalhotra, VCSR Chittepu, Maria Eugenia Jaramillo Flores*

IPN - Escuela Nacional de Ciencias Biológicas

Chronic degenerative diseases today are epidemiologically the most important, that affect most of the populations. Diabetes is one of the chronic degenerative disease. Diabetes mellitus (DM) a metabolic disorder because of insufficient insulin secretion & action elevate glucose level resulting in the abnormal metabolism of fats, carbohydrates, and proteins. Our attempt to link structure of a chemical to pathways in order to identify common genes, metabolites corresponding to prescribed drugs of diabetes helped us to cluster some pathways of interests. Bioinformatics helped us to link chemical structure to metabolic pathways and genes involved. Computational Databases like KEGG, PubChem, Drug Bank were used to collect information about prescribed drugs, metabolic pathways, and genes involved. We identified most of the prescribed drugs, involved in regulating glycerophospholipid metabolism and others. We would be presenting regarding glycerophospholipid metabolism and some common genes. Identified genes would be tested in future for validation of biomarkers for diabetes in animal models, patient samples from hospitals.

Development of a multi-modular boolean network for the study of acute lymphoblastic leukemia

Aug 3rd
4:00 pm

Jennifer Enciso[1,2]; Elena R Alvarez-Buylla[3,4]; Rosana Pelayo[1]

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B-cell precursors ALL (B-ALL) is the most common cause of death for cancer among pediatric patients. However, despite major advances, the etiology and progession of leukemia are yet to be unraveled. Leukemogenesis of B-ALL appear to be an emergent event of deregulated modules involved in the determination of cell cycle progression, early B lymphopoiesis, and communication with BM microenvironment. The reconstruction of these three modules and their analysis as boolean models will provide useful information about the altered processes that lead in an increase of B-ALL cells fitness, which are known to be capable for replacing normal hematopoietic cells through a process that may involve the remodelation of hematopoietic microenvironment.

Aug 3rd
4:00 pm

Machine Learning approach for antimicrobial compound prediction

Erika Alejandra Peláez Coyotl[1]; Gabriel del Río Guerra[1]

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Antimicrobial peptides (AMPs) are promising drugs because of their multiple functions such as broad spectrum against bacteria, fungi, viruses, antitumoral properties and contraceptive functions. Nonetheless discovery of effective AMPs is hampered by their rapid degradation and little structural stability that reduces or abolishes their activity. Finding non peptidic small molecules with similar properties to AMPs could assist in this endeavor. We introduce a new method that can predict colourants with antimicrobial properties. Here, classifiers trained with an AMP dataset are able to identify colourants with reported antimicrobial activity with high accuracy. We expect this approach to be a good alternative to AMPs discovery.

Aug 3rd
4:00 pm

Including physical forces in the network of molecules involved in the control of blood vessel growth and remodeling

Nathan Weinstein[1]; Karla Gisela Pedroza-Ríos[2]; Edgar Nathal[3]; Marco Zenteno[3]; Feliú Sagols[1]; Isidoro Gitler[1]; Jaime Klapp[1,4]

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The molecular regulatory network involved in blood vessel growth, remodeling and artery-vein differentiation interacts with shear stress and mechanical stretch. These interactions are very important during the formation of the circulatory system. The interactions are also important regulators of the response to exercise training, the accumulation of cycles in the blood vessel network through the lifetime of a person and proper wound healing. We have simulated the dynamic behavior of a minimalistic logical discrete model of the molecular network including the relevant molecules, shear stress and mechanical stretch., in order to explore the dynamic implications of the interaction between the molecular network and the mechanical forces.

Aug 3rd
4:00 pm

Predicting gene expression changes in Retinal Pigment Epithelial Cells using a Network Signal Propagation and Genetic Perturbation Approach

César Miguel Valdez Córdova, Benjamin Tovar Cisneros, Victor Manuel Treviño Alvarado

Tecnológico de Monterrey, Campus Monterrey

We present Network Signal Propagation and Genetic Perturbation, a computational model that uses the gene expression as the cell state and protein-protein interaction (PPI) information weighted from gene expression to predict gene activation and expression changes in a particular cell type arising from a specific stimulus. For this, we propagate the stimulus through the PPI network until convergence is reached and use the activation values to estimate gene expression changes based on genetic regulatory networks. While we could not recover all differentially expressed genes, we could partially explain gene differences in the process following cellular stimulation.

Mouse Mammary Tumors induced by Virus

Aug 3rd
4:00 pm

Maria L. Streber[1], Juan Carlos León[2], Alejandro Zentella[3], Jose Luis Ventura[4]

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Mammary tumors in mice are scare, depend of genetic background. In our experience, spontaneous murine tumors are rare, so we decided to study them and establish primary cell cultures to compare the findings to the MET among primary tumors, cell culture and re-implanted. Four-teen spontaneous mammary tumors in mice were studied from Arabic strain (Fancy mice), which were developed only in adult females at the end of their reproductive cycle. Animals were selected by subcutaneous nodules, with a size more than 1 cm in diameter, the body weight was recorded, weight of each tumor were recorded and its dimensions were measured with a vernier. Electronic cell culture, light microscopy and transmission, cellular imprints samples were collected. Four primary tumors were used for cell cultures. At least 2 passages were conducted for reseeding and a more uniform population of neoplastic cells was obtained. Spontaneous tumors and cell cultures were analyzed by TEM, using 2% glutaraldehyde fixative in cacodilate buffer. Sections were viewed with an electron microscope Fei Tecnai Biotwin at 80kV. In phase contrast microscopy the cell monolayer cultures were observed as luminal secretory cells with secretory vesicles in their cytoplasm, TEM cells in culture have provided much detail. Viral particles could be detected close to nuclear membrane. Spontaneous tumors histologically showed a glandular pattern.

Extracellular small RNAs during parasite-host communication

Aug 3rd
4:00 pm

Ovando-Vazquez C[1], Chow F[2], Koutsovoulos G[2], Maity T[3], Blaxter M[2], Claycomb J[3], Buck AH[2], Abreu-Goodger C[1]

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We performed high-throughput sequencing of small RNA libraries from the exosome and supernatant of H. polygyrus secretory products. We also used long single-molecule sequencing (PacBio) to improve the genome assembly and annotation of H. polygyrus. This allowed us to determine the genomic locations and characterization of the secreted small RNAs. Certain classes of RNAs are enriched in exosomes, including short and full-length yRNAs, ^{22}G siRNAs, microRNAs, and specific fragments from tRNAs and rRNAs. Particularly interesting are ^{22}G siRNAs, produced by RNA-dependent RNA polymerases, suggesting that a complex RNA-interference machinery is involved in producing the exosome content.

Dormant tumor cells in ret transgenic mouse melanoma model and their interaction with memory T cells

Aug 3rd
4:00 pm

Fernando Flores-Guzmán[1,2]; Viktor Umansky [1]

[1] German Cancer Research Center (DKFZ)
[2] Universidad de la Costa

Melanoma resistance to chemo- radio- and immunotherapy has been attributed to the presence of either cancer stem cells or dormant tumor cells. Using a transgenic mouse melanoma model, CD133+ melanoma cells represent less than 1.5% of all cells in primary skin tumors, exhibit stemness, metastatic, angiogenic and immunosuppressive profile compared to their $CD133^-$ counterparts. Mice older than 20 weeks without macroscopic tumors contain in the bone marrow (BM) tyrosinase related protein (TRP)-2-specific effector memory CD8+ T cells and show no further melanoma progression. BM memory CD8+ T cells were co-localized with TRP-2+ dormant melanoma cells in mice without macroscopic tumors. CD133+ melanoma cells induced immunosuppressive mechanisms.

DOR motifs and their relationship with robustness

Aug 3rd
4:00 pm

Roberto Galindo Ramírez[1]; Gabriel del Río[1]

[1] Instituto de Fisiología Celular, UNAM, MX

The understanding of stable behavior associated phenomena is a relevant topic in biology. Particularly, boolean networks have been used to understand the transcription dynamics and how it can generate states known as attractors, which are seen as steady states in cellular processes. It has been observed that Saccharomyces cerevisiae transcriptional regulatory response contains differential distribution of motifs depending on the stimuli to which is subjected, one of them is Dense Overlapping Regulon (DOR). In this work we analize the effect caused by the introduction of one DOR motif in boolean system dynamics. We found that DOR promotes robustness in specific attractors and are present in response to stress in yeast cells.

Role of miRNAs in breast cancer regulatory networks

Aug 3rd
4:00 pm

Diana Drago-García, Jesús Espinal-Enríquez, Enrique Hernández-Lemus

INMEGEN

Breast cancer is a complex disease with transcriptional alterations as one of its main features. MiRNAs are small non coding RNAs related to the transcriptional regulation of genes involved in many cellular processes with some of them specifically associated to breast cancer. To understand the transcriptional relation between miRNAs and genes we constructed Mutual Information networks with sequencing data from TCGA breast cancer samples. Network architectures are different between cases and controls as well as their regulation. The cases network highest degree miRNA family is mir-199 and mir-200 for controls, these miRNAs first neighbors are linked to Epithelial-Mesenchymal transition genes which are important for cancer pathogenesis.

A framework for studying the information flow between transcriptional regulation and metabolism in Escherichia coli K-12.

Aug 3rd
4:00 pm

Daniela Ledezma-Tejeida; Julio Collado-Vides

Centro de Ciencias Genómicas, UNAM

It is often assumed that Transcription Factors (TF) in bacteria regulate individual Biological Processes. We quantified the uniformity of the metabolic impact of 189 local TFs. Only 18% are involved in linear metabolic fluxes even if metabolic pathways are used to find relations among apparently disconnected fluxes. We propose an information flow based model termed Genetic Sensory Response Unit (GENSOR Unit) to describe the processing of a signal by a TF: signal detection, transformation into an effector, change in gene expression levels and resulting metabolic effect. GENSOR Units are the building blocks used by the cell to respond to changes and can be used as stepping-stones for understanding the interplay between levels of complexity.

Effect antiproliferative of (-)-epicatechin and its relationship with Reactive Oxygen Species in breast cancer cell

Aug 3rd
4:00 pm

Adriana Guadalupe Perez Ruiz[1]; Ivonne María Olivares Corichi[1]; José Rubén García Sánchez[1]

[1] **Postgraduate Studies and Research Section, School of Medicine at National Polytechnique Institute, Mexico**

Breast cancer is the neoplasia of increased morbidity and mortality. Our research group has shown that (-)-epicatechin present an antiproliferative effect in cell lines from breast cancer. Cancer cells have an increased metabolism, which induce higher production of reactive oxygen species (ROS). However cancerous cells are able to evade the damage by ROS, process that it has been related with the overexpression of a protein called uncoupling protein 2 (UCP2). The data obtained in this work, suggest that the effect antiproliferative of (-)-epicatechin is mediated by an induction of apoptosis, an increase in the production of ROS, decreasing of antioxidant defenses and downregulation in UCP2 expression.

An Orthology Quality Measure

Aug 3rd
4:00 pm

Maribel Hernández Rosales, Sarah Berkemer, Gabriel Moreno Hagelsieb, Peter, Stadler

Conacyt Fellow, Institute of Mathematics, UNAM Juriquilla; University of Leipzig; University Wilfried Laurier; University of Leipzig

Here we present a graph-theory based analysis of the quality of predicted orthologous relationships. We have applied this method to sets of genes from the Escherichia coli pan genome. It has been proven that a graph representing valid orthology relationships must be a cograph. A cograph is a graph where no induced subgraph in four vertices forms a path, called a P4. Forbidden sugraphs are induced subgraphs that contain more than one P4. We therefore explored the clusters of genes representing the Escherichia coli pangenome and measured their consistency. We suggest that the existence of many forbidden subgraphs in some clusters might be mostly due to horizontal gene transfer, gene fusion and gene fission.

Aug 3rd
4:00 pm

Computational model of the intracellular dynamics of calcium in electrically coupled pancreatic beta cells during glucose stimulation

Gerardo J. Félix-Martínez and J. Rafael Godínez-Fernández

Department of Electrical Engineering, Universidad Autónoma Metropolitana

We present a mathematical model of the spatiotemporal distribution of intracellular Ca2+ in electrically coupled insulin-secreting pancreatic beta cells in response to glucose stimulation. We evaluated how the geometrical properties of the simulated cells could affect the synchronized behavior of the membrane potential and intracellular Ca2+. In addition, we have also analyzed how endogenous Ca2+ buffers could modify the synchronized dynamics of Ca2+ depending on their binding properties. The resulting model consists of a detailed mathematical representation of the electrical activity coupled to a reaction-diffusion model of the spatiotemporal distribution of Ca2+ for each cell included in the simulated clusters.

Aug 3rd
4:00 pm

Mathematical modeling of bacterial intergenic regions with pattern recognition methodologies

Veronica Jimenez-Jacinto[1]; Getzabeth Gonzalez[1]

[1]Instituto de Biotecnología, Universidad Nacional Autonoma de Mexico

we present the mathematical modeling for the description of intergenic regions for bacterial annotated organisms. In order to make predictions of biological objects not described, or not recorded, as the small RNAs, transcription start sites, or discovery of new genes, coverage of RNAseq data and methodology of Pattern Recognition are used. This allows to automatically locate regions with coverage that could be associated with objects of interest, gathering information of the intergenic regions, ranging from the trend of the coverage, depth, type of intergenic region, etc. The aim of the model is to locate behaviors indicating the presence of non-annotated biological elements of interest.

Aug 3rd
4:00 pm

Modeling metabolic pathways of human protozoan parasites

Emma Saavedra

Departamento de Bioquímica, Instituto Nacional de Cardiología. Mexico City, MEXICO.

Kinetic modeling of metabolic pathways, a bottom-up Systems Biology approach, build models starting from the knowledge of the kinetic and thermodynamic properties of their isolated enzymes, transporters and reaction steps. These models help to the understanding of the controlling and regulatory mechanisms that underlies in the function of a metabolic network. We have built kinetic models of the energy and antioxidant metabolism of the human parasites Entamoeba histolytica and Trypanosoma cruzi, the causal agents of human amebiasis and American trypanosomiasis, respectively. By this strategy we were able to identify the main controlling enzymes which can be proposed as the more convenient targets for therapeutic intervention.

Mathematically modelling memory in neural tube transcriptional regulation

Aug 3rd
4:00 pm

Edgar Herrera Delgado[1,2]; James Briscoe[1]; Peter Sollich[2]

[1]The Francis Crick Institute, UK
[2]King's College London, UK

In the neural tube a gradient of the morphogen Sonic Hedgehog (Shh) controls the spatial pattern of gene expression. This gradient is interpreted by a transcriptional network that leads to distinct cell fates depending on the concentration and duration of Shh exposure. We have mathematically modelled this network, and by combining the Fokker-Planck equation with a Zwanzig-Mori projection separated it into subnetwork and bulk to understand the importance of the different parts. We confirmed predictions from this method by comparing with numerical simulations and with in vivo patterns of expression. This tool provides an unbiased way of determining the importance of network interactions and yields predictions that can be tested experimentally.

Metabolic Attractors in Cancer: A Systems Biology approach

Aug 3rd
4:00 pm

Jorge A. Guadarrama-Orozco

Translational Medicine Laboratory. National Cancer Institute.

Metabolism is described as an emerging hallmark, reflecting a sense of ambiguity (neither core nor enabling) concerning the role of metabolism in cancer development. We propose the study of cancer attractor hypothesis based on theory of complex gene regulatory networks (GRN) that control cell fates and that the premalignal cell gets in a pathological cancer attractor state of GRN. Certain proteins function are related in different metabolic pathways and intercellular signaling environmental cues allowing to enter the premalignant metabolic profiles as a meta-stable cancer attractor in GRN. Finding this attractors during cellular stress, could lead us to a more accurate prevention and drug development before the disease manifested.

Thursday August 4^{th}

Oral session

Aug 4th
9:00 am

Insulin impact on the CD4+ T lymphocyte regulatory network mediates inflammatory responses during acute hyperinsulinemia

M.E. Martinez-Sanchez[1,2], M. Hiriart[2,3], E. R. Alvarez-Buylla[1,2]

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[2]Centro de Ciencias de la Complejidad, Universidad Nacional Autónoma de México
[3]Departamento de Neurodesarrollo y Fisiología, Instituto de Fisiología Celular, Universidad Nacional Autónoma de México

Obesity is linked to insulin resistance, hyperinsulinemia, chronic inflammation, and alterations in the behavior of CD4+ T cells. We used a dynamic regulatory network model to study the interaction between the network underlying CD4+ T cell fate attainment, the micro-environment and the level of insulin. In the presence of high levels of insulin Th17 and Th1 become more stable and their basin sizes are augmented, IL10+ regulatory T cells become less stable or disappear, while TGFB+ cells remain unaltered. The model helps understand the apparently paradoxical role of TGFB and the emergence of the fat Treg phenotype. This work highlights the importance of using a system-level approach to study complex diseases like metabolic syndrome.

Aug 4th
9:30 am

The Pathobiological Complexity of Childhood Cancer: Acute Lymphoblastic Leukemia as a Paradigm for Integrative Research

Rosana Pelayo

Lymphopoiesis Lab, Oncology Research Unit. Instituto Mexicano del Seguro Social. México

Our understanding of the pathobiology of cancer has substantially advanced due to novel theoretical and experimental integrative strategies leading to a more complex, dynamic and interactive network perspective where genetics is in constant dialogue with micro and macro environmental cues that contribute to the etiology and maintenance of malignant cells.

Acute lymphoblastic leukemias are the most frequent childhood malignancies and a foremost cause of mortality worldwide. Even though efficient therapeutic agents have been developed that increased the overall survival rates, factors such as leukemic cell infiltration, resistance to therapy and relapse remain an obstacle to curing patients. Clonal diversity and the tumor-initiating abilities of multiple differentiation stages retaining stemness and plasticity properties highlight its complexity and the uncertainty of its cell origins. Moreover, a pro-inflammatory microenvironment creating abnormal niches may expose cells to prolonged proliferation and contribute tumor progression. By unraveling the biological identity of cancer precursor cells and of the regulatory mechanisms facilitating its permanence at the time we construct multi-cellular multi-compartment mathematical models, we may better simulate the behavior of the disease and predict outcomes to further assist proper treatment decisions.

Key Words: *Acute lymphoblastic leukemia; Tumor microenvironment; Leukemia initiating cells; Early lymphoid development; Cancer biology*

A systems biology approach to understand and prevent complex epithelial tissue diseases

Aug 4th
10:30 am

Elisa Domínguez Hüttinger[1,4], Francisco J. Reyes Mora [2], Reiko J. Tanaka [3], Juan Carlos Martínez García [4], and Elena Álvarez-Buylla Roces [1]

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[2] Faculty of Sciences, National Autonomous University of Mexico, Mexico City, Mexico
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[4] Center for Complexity Sciences, National Autonomous University of Mexico, Mexico City, Mexico.

In Mexico, most deaths are caused by epithelial tissue diseases, including carcinomas, allergic diseases, and infections of mucosal surfaces. There is thus an urgent need for improving the current strategies for prevention, diagnosis and treatment of these diseases. Specifically, better treatments that 1) effectively tackle the patient-specific causes of the disease 2) halt the pathogenic progression before the onset of late and severe symptoms, and 3) minimize the unwanted side effects, are required. We propose an integrative systems biology approach to systematically assess the role of the different pathogenic and pharmacological factors on the onset, progression, prevention and reversal of epithelial tissue diseases, from an integrative, dynamic and quantitative perspective. It is a mathematical representation of the complex regulatory interplays that exist between the epithelial phenotype, inflammation and infection, with which we integrate and analyse different experimental and clinical datasets, both from the literature and from our collaborators. Applying this framework to study atopic dermatitis, pneumonia, and hepatocarcinoma, we could 1) identify previously unknown disease mechanisms underlying their onset and progression, 2) dynamically describe the gradual development from a pre-clinical to a severe disease phenotype, and 3) propose personalized treatment regimes that minimize the treatment effort while effectively halt or reverse the progression of these diseases.

The mathematical epidemiology of infectious diseases: the cases of Zika, Dengue and leptospirosis

Aug 4th
11:30 am

Jorge Velasco

Instituto de Matemáticas Unidad Juriquilla, UNAM

In this talk we present a general overview of the epidemics of Zika, Dengue an Chikungunya that currently occur in the Americas. We present a series of mathematical models that have been constructed to theoretically explore the peculiar dynamics that the interactions between these three viruses present. In particular we address the problem of coexistence and the roles of sexual and vector transmission in the spread of these diseases.

Aug 4th
12:30 pm

Circadian control of metabolism: a metabolomics approach

Ricardo Orozco Solis

INMEGEN

During the past few years, metabolomics has emerged as a powerful strategy to find gain insights on organismal and cellular homeostasis, and how organisms responds to external stimuli and/or pathological conditions. Therefore, one of the main challenges on system biology is to integrate transcriptional, protein and metabolic networks, to understand how cells respond to environmental challenges. Importantly, metabolomics has allowed us to decipher which metabolites impinge in a number of key intracellular pathways through their interactions with regulatory proteins, including transcription factors, nutrient sensors, epigenetic regulators or rate limiting enzymes. Yet, most of biological processes are under the control of the circadian clock, a molecular machinery which imposes daily rhythms into the pace of major cellular responses. Therefore, the integration of these networks considering the additional regulatory layer elicited by circadian rhythmicity results of pivotal importance to better understand how metabolism and molecular responses interplay through time. "Circadiomics" is a systems biology platform consisting on a computational resource integrating circadian transcriptomics, proteomics and metabolomics data sets to investigate and predict how the circadian clock modulates metabolism on different experimental paradigms.

Aug 4th
13:00 pm

Network-based Dynamic Modeling and Control Strategies in Complex Diseases

Jorge Gómez Tejeda Zañudo

University of Pennsylvania

In order to understand how the interactions of molecular components inside cells give rise to cellular function, creating models that incorporate the current biological knowledge while also making testable predictions that guide experimental work is of utmost importance. To model the dynamics of the networks underlying complex diseases we use network-based models with discrete dynamics, which have been shown to reproduce the qualitative dynamics of a multitude of cellular systems while requiring only the combinatorial nature of the interactions and qualitative information on the desired/undesired states.

Here I present some recently developed analytical and computational methods for analyzing network-based models with discrete dynamics. The method presented is based on a type of function-dependent subnetwork that stabilizes in a steady state regardless of the state of the rest of the network, and which we termed stable motif. Based on the concept of stable motif, we proposed a method to identify a model's dynamical attractors, which are identifiable with the cell fates and cell behaviors of modeled organisms. We also proposed a stable-motif-based control method that identifies targets whose manipulation ensures the convergence of the model towards an attractor of interest. We illustrate the potential of these methods by collaborating with wet-lab cancer biologists to construct and analyze a model for a process involved in the spread of cancer cells (epithelial-mesenchymal transition), and also applied them to several models for complex diseases, such as a type of white blood cell cancer (T-LGL leukemia). These methods allowed us to find attractors of larger models than what was previously possible, identify the subnetworks responsible for the disease and the healthy cell states, and show that stabilizing the activity of a few select components can drive the cell towards a desired fate or away from an undesired fate, the validity of which is supported by experimental work.

Index