TALLER

ANÁLISIS Y CONTROL DE SISTEMAS BIOLÓGICOS INTERCONECTADOS

13 y 14 de Octubre, 2016
UNAM Juriquilla

Conferencia plenaria: Controlling the human microbiome
Yang-Yu Liu (Harvard)

Platicas invitadas:

Roberto Alvarez (UAQ)
Alfredo Varela (Neurobiologia-UNAM)
Fernando Castaños (CINVESTAV)
Guillermo Santiago (IM-UNAM)
Fernando López-Caamal (UGTO)
Ana Gabriela Gallardo (IMSS)
Ayari Fuentes-Hernandez (CCG-UNAM)
Leonid Fridman (FI-UNAM)
Isaac Chairez (UPIBI-IPN)
Jose Luis Aragon (CFATA-UNAM)
Yu Tang (FI-UNAM)
Alejandro Vargas (II-UNAM)
Marco Tulio Angulo (IM-UNAM)

***Becas de alojamiento para estudiantes**

Organizadores: Marco Tulio Angulo y Jorge X. Velasco
Informes: mangulo@im.unam.mx

Instituto de Matemáticas

CONACYT

WORKSHOP ON ANALYSIS AND CONTROL OF BIOLOGICAL NETWORKED SYSTEMS
UNAM Juriquilla, October 13 and 14, 2016

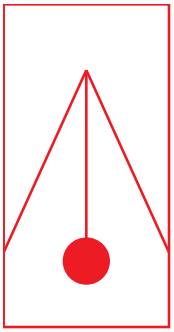
Instituto de Matemáticas

Motivation. From controlling gene regulation processes of cells to restoring the microbiome in our gut from dysbiosis back to its healthy state, the potential behind controlling biological systems has never been this big before. Yet, the puzzling complexity of biological systems —often consisting of a manifold of different components (genes, proteins, species, etc.) interacting trough complex networks— calls for new control and system theoretic approaches, relying on other disciplines such as network science and mathematical biology.

This workshop brings together leading national and international researchers working on a rapidly emerging field at the intersection of control theory, mathematical biology and network science. We are pleased to announce the very diverse background of our participants, from engineering to physics, and neuroscience to medicine.

We hope you enjoy the workshop!

—The organizing committee



Venue. The workshop will take place at the *Laboratorio Nacional de Visualización Cientifica Avanzada* (National Laboratory for Advanced Scientific Visualization), UNAM, Juriquilla.

Hotels. The official hotel for the workshop is *Encore Queretaro* (**encorequeretaro.com**). You will receive an email with your room number and further details before October 10.

Transportation and meals. Breakfast is included with your hotel reservation. The hotel will also provide transportation to the UNAM campus and back to the hotel. Lunch will be served at the *Centro Cultural Universitario (CAC)*, that is at walking distance from the venue of the workshop.

PROGRAM

hour	Thursday 13
9:35	Shuttle from Hotel to UNAM
10 — 10:10	Welcome and overview (Jorge X. Velasco)
10:10 — 10:20	Introduction by Workshop Organizers (Marco Tulio Angulo)
10:20 – 11:10	Plenary talk (Yang-Yu Liu, Harvard)
11:10 - 11:45	Talk 1 (Roberto Alvarez, UAQ)
11:45 — 12	BREAK
12 — 12:35	Talk 2 (Alfredo Varela, Neurobiologia UNAM)
12:35 — 1:10	Talk 3 (Fernando Castaños, CINVESTAV)
1:10 — 1:30	BREAK
1:30 — 2:05	Talk 4 (Guillermo Ramírez-Santiago, IM-UNAM)
2:05 —4:00	LUNCH + discussion/coffee at the venue
4:00 - 4:35	Talk 5 (Fernando Lopez-Caamal, UGTO)
4:35 - 5:10	Talk 6 (Ana Gabriela Gallardo, IMSS)
5:10 - 5:40	Discussion & daily wrap-up
5:40	Shuttle from UNAM to Hotel

hour	Friday 14
9:35	Shuttle from Hotel to UNAM
10 — 10:35	Talk 1 (Ayari Fuentes-Hernandez, CCG-UNAM)
10:35 — 11:10	Talk 2 (Leonid Fridman, FI-UNAM)
11:10 — 11:30	BREAK
11:30 — 12:05	Talk 3 (Isaac Chairez, UPIBI-IPN)
12:05 - 12:40	Talk 4 (Jose Luis Aragon, CFATA-UNAM)
12:40 - 1	BREAK

hour	Friday 14
1:00 — 1:35	Talk 5 (Yu Tang, FI-UNAM)
1:35 — 2:10	Talk 6 (Marco Tulio Angulo, IM-UNAM)
2:10 — 4:10	LUNCH
4:10 — 4:45	Talk 7 (Alejandro Vargas, II-UNAM)
4:45 — 5:00	Discussion, final wrap-up.

LIST OF ABSTRACTS (NO PARTICULAR ORDER)

Roberto Álvarez-Martínez (ralvarez@ciencias.unam.mx)
Unidad de Microbiología Básica y Aplicada, Facultad de Ciencias Naturales Universidad Autónoma de Querétaro

Title: Inferring MicroRNA Functions Using Co-expression Networks: Regulation Beyond Direct Targets

Abstract: MicroRNAs (miRNAs) are small non-coding RNA molecules that post-transcriptionally regulate gene expression by binding to partially complementary sites in 3'UTRs [1]. They are highly abundant in most animals, with the human genome encoding around 2,000 according to the latest annotation. Collectively, they are predicted to target more than 50% of mammalian coding genes. Many of them are highly conserved across bilaterian organisms, and miRNA regulation is increasingly recognized as a key player involved in a variety of biological processes, from development to disease. Most research on miRNA function has focused on the discovery of direct targets, *i.e.* mRNAs that are directly bound by a miRNA. So far, however, no one has systematically explored genes that are indirectly regulated by miRNAs. This work addresses this problem, using computational methods.

We first analyze mRNA profiling experiments (microarrays or RNA-Seq) that study the effect of over-expressing a miRNA. In these experiments we expect to find the biological processes that are affected by the miRNA. In addition to direct targets being down-regulated, other mRNAs with no miRNA binding site are also down-regulated. We call these indirect targets "co-targets". The experiments also show mRNAs that are up-regulated upon miRNA over-expression, and we call these "anti-targets". In order to find anti-targets we first cluster the whole network and localize the cluster that is enriched in direct targets for a single miRNA. We then predict that the most distant cluster from this point should be enriched in anti-targets.

In order to confirm our results we used RNA-Seq data from several human tissues and observe which functions are down/up regulated due to a miRNA effect. From our predictions, up-regulated targets (anti-targets) are related to functions conferring tissue specificity. Our results highlight the importance of studying both classes of targets to understand the global function of microRNAs.

Yang-Yu Liu (spyli@channing.harvard.edu)
Channing Division of Network Medicine
Brigham and Women's Hospital and Harvard Medical School

Title: Controlling human microbiota

Abstract: We coexist with a vast number of microbes—our microbiota—that live in and on our bodies, and play an important role in human physiology and diseases. Propelled by metagenomics and next-generation DNA sequencing technologies, many scientific

advances have been made through the work of large-scale, consortium-driven metagenomic projects. Despite these advances, there are still many fundamental questions regarding the dynamics and control of microbiota to be addressed. Indeed, it is well established that human-associated microbes form a very complex and dynamic ecosystem, which can be altered by drastic diet change, medical interventions, and many other factors. The alterability of our microbiome offers opportunities for practical microbiome-based therapies, e.g., fecal microbiota transplantation and probiotic administration, to restore or maintain our healthy microbiota. Yet, the complex structure and dynamics of the underlying ecosystem render the quantitative study of microbiome-based therapies extremely difficult. In this talk, I will discuss our recent theoretical progress on controlling human microbiota [1,2].

[1] Gibson TE, Bashan A, Cao H-T, Weiss ST, Liu Y-Y. On the Origins and Control of Community Types in the Human Microbiome. *PLOS Computational Biology* 2016;12 (2):e1004688.

[2] Bashan A, Gibson TE, Friedman J, Carey VJ, Weiss ST, Hohmann EL, Liu Y-Y. Universality of Human Microbial Dynamics. *Nature* 2016;534:259-262.

Leonid Fridman (lfridman@unam.mx)
Facultad de Ingeniería, UNAM

Title: Controlling uncertain system with minimal knowledge: the notions of practical relative degree and sliding mode control

Abstract: As we move forward trying to control increasingly complex systems such as biological ones, our uncertainty of their dynamics quickly increase. This natural increase of uncertainty makes the design of efficient control algorithms much more challenging. In this talk, I will describe a recent methodology to control arbitrary uncertain systems requiring to know two parameters of them only: the so-called "practical relative degree" and "bounds" for their dynamics. These two parameters can be easily inferred from very basic experiments of the response of the system to be controlled against available control actions. Finally, based on the inferred parameters, I will show how the "sliding mode control" methodology provides ready-to-use controllers with mathematical guarantee of good performance. The proposed approach is illustrate on the glucose regulation problem of diabetic patients.

Fernando Castaños (fcastanos@ctrl.cinvestav.mx)
Departamento de Control Automatico, CINVESTAV, IPN

Title: Implementing robust neuromodulation in neuromorphic circuits

Abstract: We introduce a methodology to implement the physiological transition between distinct neuronal spiking modes in electronic circuits composed of resistors, capacitors and transistors. The result is a simple neuromorphic device organized by the same geometry and exhibiting the same input–output properties as high-dimensional electrophysiological neuron models. Preliminary experimental results highlight the robustness of the approach in real-world applications.

Jose Luis Aragon (aragon@fata.unam.mx)
CFATA, UNAM Juriquilla

Title: Quasiperiodicity and chaos in reaction-diffusion and ventricular fibrillation

Abstract: We first show that a model reaction-diffusion system with two species in a monostable regime and over a large region of parameter space produces Turing patterns coexisting with a limit cycle which cannot be discerned from the linear analysis. The patterns oscillate in time and when varying a single parameter, a series of bifurcations leads to period doubling, quasiperiodic, and chaotic oscillations. We also show that this reaction-diffusion system can be discretized in such a way that a set of three nonlinear oscillators is obtained. This discretized model is capable to reproduce electrocardiogram signals of healthy hearts as well as under several well-known rhythm disorders. In particular it is shown that under ventricular fibrillation, the electrocardiogram signal is chaotic and, as in the continuous case, the transition to from sinus rhythm to chaos is consistent with the quasiperiodic (Ruelle-Takens-Newhouse) route to chaos, as experimental studies indicate.

Marco Tulio Angulo (mangulo@im.unam.mx)
Instituto de Matemáticas, UNAM Juriquilla

Title: Taming complexity: analysis and control of complex systems in biology and medicine.

Abstract: Instead of being an overwhelming obstacle, complexity —understood as the manifestation of interconnectedness of beings and things in and around us— can play in our favor, if we are able to harvest its potential. In this talk, I will discuss two case studies showing how the structure of this complexity —natural described in terms of networks— leads to rigorous analysis and control of diverse complex systems. First, I will discuss how networks are the missing ingredient to obtain a "qualitative theory of stability" of general nonlinear systems —in the spirit of René Thom's work— opening the door to study stability by knowing the signs of the interactions (activation or inhibition) in the system only. In the second part of the talk, I will discuss our ability to control the microbial communities in and around us —commonly known as microbiomes— that play key roles in our and Earth's physiology. At a given site (e.g. our gut), these microbial communities

consists of trillions of different species, interacting in very complex manners. I will show how the intrinsic ability to take control of the whole state of a microbiome trough manipulating a few selected species —the "driver species"— is encoded by the networks underlying these ecological communities. This finding allows us to quickly identify those driver species from the very limited knowledge of microbiomes we currently have, opening an unexpected door to address a variety of problems from treating disease to global warming to sustainable agriculture.

[1] M.T. Angulo and J.J-. Slotine. "Qualitative stability of nonlinear networked systems", https://arxiv.org/abs/1603.06483

Guillermo Ramírez-Santiago (gramirez@im.unam.mx)
Instituto de Matemáticas, UNAM Juriquilla

Title: Describing chemical neurotransmission with a kinetic model

Abstract: Recent experimental observations in presynaptic terminals at the neuromuscular junction strongly suggest the existence of stereotyped vesicles patterns in the exocytosis of neurotransmitters. They appear as a result of the complex collective molecular interactions that take place in the chemical synapsis. Vesicles are found positioned in four states: pool, docking, priming, and fusion. This positioning of the vesicles gives rise to a cooperativeness morphological pattern. Taking into account these observations we have proposed a kinetic model to describe the neurotransmitter exocytosis process. Each vesicle state is represented by a kinetic state so that the process can be analyzed as a chain of four coupled chemical reactions. The kinetics of these reactions is analyzed quantitatively by means of a Stochastic Kinetic Equation. We have been able to reproduce the response of the neuromuscular synapses observed in mammals and amphibious. We obtained the basal neurotransmitter release in the absence of stimulation, the evoked response to an electric stimulus, and the phenomena of facilitation and depression. The model considers the molecular interactions as a result of the vesicles stereotyped patterns that yield the cooperativeness during the neurotransmitter release. It offers a new perspective to understand the underlying phenomena in chemical neurotransmission.

Fernando López-Caamal (fernando.lopez@ugto.mx)
Departmento de Ingenieria Quimica, Universidad de Guanajuato

Title: Two Biologically-Inspired Problems Studied via Control Theory Methods: Positive Feedback Loops Stability and Cumulative Signal Transmission

Abstract: The spirit of this talk dwells in the use of control theory methods to address, in both a qualitative and quantitative fashion, two problems in cellular biology. The first problem consists on determining stability conditions of a positive feedback with an

arbitrary number of subsystems with the same reaction topology; all of them interconnected as a positive feedback. By availing of the Small Gain Theorem we derive (necessary) and sufficient conditions, in terms of the reaction parameters, of both steady states the reaction network exhibits. Such results have direct applicability to the study of apoptosis onset: a type of cellular dead. Now, the second problem deals with the analytical computation of selected trajectories' integrated response. We focus on a class or reaction(-diffusion) nonlinear system. The resulting formulae unveil the core mechanisms implicated with signal transmission in systems; in particular we study the EGF receptor mechanism in cellular membranes and the progression of calcium ion signals in a class of (non-excitable) glial cells. We foresee that these results may assists on respirometry studies.

[1] López-Caamal, Fernando, Richard H. Middleton, and Heinrich J. Huber. "Equilibria and stability of a class of positive feedback loops." Journal of mathematical biology 68.3 (2014): 609-645.

[2] Oyarzún, Diego A., et al. "The EGFR demonstrates linear signal transmission." Integrative Biology 6.8 (2014): 736-742.

[3] Lopez-Caamal, Fernando, et al. "Spatial Quantification of Cytosolic Ca Accumulation in Nonexcitable Cells: An Analytical Study." IEEE/ACM Transactions on Computational Biology and Bioinformatics 11.3 (2014): 592-603.

[4] Oyarzún, Diego A., et al. "Cumulative signal transmission in nonlinear reaction-diffusion networks." PloS one 8.5 (2013): e62834.

[5] López-Caamal, Fernando, et al. "Analytic computation of the integrated response in nonlinear reaction-diffusion systems." 2012 IEEE 51st IEEE Conference on Decision and Control (CDC). IEEE, 2012.

Ayari Fuentes-Hernandez (ayarifh@ccg.unam.mx)
Centro de Ciencias Genomicas (CCG), UNAM

Title: Controlling the evolution of antibiotic resistance (in theory and in vitro)

Abstract: A fundamental engineering principle states that controlling complex dynamical systems cannot be done optimally with controls that are non-responsive and constant through time. Yet this is how we approach treatment with antimicrobial drugs. Indeed, medical textbooks state that the prolonged administration of high doses of antibiotics minimizes pathogen load and thus prevents the evolution of drug-resistant bacteria. This pre-genomic rationale stems from the notion that overdosing with antibiotics is, at worse, a therapeutically neutral choice and as a result there is no harm in taking drugs for prolonged periods. The purpose of this talk is to discuss why we believe this *'hit early and*

hit hard' treatment paradigm is responsible for one of the most challenging problems facing modern medicine: the evolution of antibiotic resistance.

In this talk we will pose a data-driven evolutionary model of an experimental microbial system that will allow us to study the spatio-temporal dynamics of drug resistance adaptation. A systems-pharmacology model based on molecular and kinetic assumptions of the interactions between drugs and their targets will be used as the core of a population-genetics model describing the ecological dynamics of different bacterial sub-populations competing for a single limiting resource in a multidrug environment. Using results from control and systems theory we will show, both theoretically and experimentally, that multidrug environments can support a dynamic and heterogeneous bacterial population structure, and consequently the best treatment strategies have to be, as the bacteria we are trying to kill, adaptive in time. Furthermore, we will use this evolutionary pharmacogenetics model to evaluate the efficacy of different drug deployment strategies with the aim of designing optimal sequential treatments (that alternate the use of different antibiotics) in order to control the evolution of antimicrobial resistance.

Alejandro Vargas (AVargasC@iingen.unam.mx)
Instituto de Ingenieria, UNAM

Title: Process control applications for wastewater treatment: simple controllers for a complex process

Abstract: Environmental bioprocesses such as biological wastewater treatment are complex. Several types of microorganisms interact with each other to biotransform organic compounds present in the water and degrade them to simpler compounds or products of interest, such as biogas or innocuous biomass. The mathematical description of the processes can become quite complex, even if simplifications are made, such as lumping or the assumption of perfect mixing conditions. Usual descriptions involve a set of algebro-differential equations that describe the dynamics of microorganism growth and decay, as well as degradation of substrate, production of useful compounds, and other physicochemical transformations. Furthermore, for a complete description, several unit processes must be linked. This leads to large nonlinear systems with many parameters that must be determined to characterize the bioprocess, which in addition may be highly time-varying or uncertain. The difficulty of obtaining experimental values for these parameters, together with the fact that it is neither possible to measure many variables on-line, nor easy to actuate on some (input) variables, poses a challenging problem for designing process controllers. However, it has been shown –even experimentally- that simple controllers may be able to ensure stability or increase performance, even despite the changing model parameters (mostly due to changes in the microbial community) or the uncertainty of measurements. This talk exemplifies some of the controllers proposed by our research group for some aerobic and anaerobic bioreactors, which have been successfully tested with laboratory experiments.

Alfredo Varela (avarela@unam.mx)
Instituto de Neurobiologia, UNAM

Title: Mutational dynamics in the mouse mitochondrial genome

Abstract: The mitochondrial genome is a double-stranded DNA molecule of which there may be up to thousands of copies per cell which are required for mitochondrial functions. Mutations of various types may occur de novo in somatic cells or be transmitted through germ line by maternal inheritance. Among these alterations, deletions are the most frequent and have been linked in humans to debilitanting and often fatal neuromuscular diseases. These alterations have been also associated to normal aging in humans, primates and rodents; controversies exist, however, regarding the stage of life in which they appear and accumulate, coexisting in heteroplasmy with wild-type genomes or causing cell disfunction or disease. In this work we demostrate a high abundance and diversity of deletions in the mitochondrial genome in the brain of healthy mice in different life stages, from embryos to aged individuals. Most of these deletions involve the loss of a single nucleotide but the deletion of kilobases in a single event was also detected; in both extremes, their presence was also detected at the RNA level. Deletions were found with frequencies that increase or decrease throughout life. Our studies reveal that the abundance of mitochondrial genetic variants are in a complex dynamic equilibrium which is part of normal development, growth, and aging.

Yu Tang (tang@unam.mx)
Facultad de Ingeniería, UNAM

Title: Adaptive observer for nonlinear dynamical systems with application to neural mass model

Abstract: The problem of estimating the states and parameters involved the system model is an important problem in control theory. Even though a variety of methodologies can be found dealing with the estimation of the states and of the parameters separately, simultaneous estimation of both states and parameters (i.e., adaptive observer design) is a challenging problem, especially for nonlinear systems. The analysis for such topic in linear systems has been extensively studied, classically the methodology consists of augmenting the state vector with the parameter one, reducing the problem to the estimation of states. This methodology can however lead to an over parametrization when the system dynamics is nonlinearly parameterized. Adaptive observer designs for nonlinear systems with a nonlinear parametrization has been emerged as an important active research area because of its wide range of applications. Many problems in engineering, biomedical topics, and neuroscience, among others are dealt with a systematic point of view where the states and parameters of the model must be estimated simultaneously for their applications. Adaptive

observers can give important information for development of new tools for applications, treatments and even get important information about the functioning of the systems. Although significant advances in the topic for linearly parametrized case (where both the states and the parameters enter the dynamics in a linear way), a few results has been reported in the literature when the system dynamics is nonlinear in states and/or parameters.

This talk focus on the design of adaptive observers for nonlinear systems when the system dynamics is nonlinear in states and/or parameters. Nonlinear contraction, a form of incremental stability which studies convergence of trajectories under a metric, is employed for the designs. Modular design is taken for developing the adaptive observer: first, a state observer and a parameter identifier are designed separately assuming the perfect knowledge based on the methodology to ensure their contraction property. Then, the adaptive observer is designed by combining the state observer and the parameter identifier with a feedback interconnection. Contraction analysis is carried out to ensure the overall system (adaptive observer) be contracting.

The methodology is applied to a simple neural mass model. There are different levels for modeling the neural dynamics that makes use of the nonlinear representation of the neuronal behavior. This model, well accepted by engineering and biomedical communities, has been used for studying some brain diseases and proposing new treatment. The purpose of design an adaptive observer for this simple neural mass model is to model the brain dynamics for movement disorder treatment, which is the topic of our further research.

[1] I. Grave, Y. Tang, ”A New Observer for Perspective Vision Systems under Noisy Measurements”, *IEEE Trans. Aut. Contr.*, Vol. 60, No. 2, pp. 503-508, DOI: 10.1109/TAC.2014.2332692, 2015.

[2] Jimenez, N; Tang, Y; M. Gonzalez, ”Identification of First- order Hammerstein Systems and its Application to a Sim- ple Neural Mass Model for Parkinson’s Disease Treatment”, *IEEE International Control Conference and Application*, 2013, Hangzhou, China.

LIST OF ATTENDEES

Profesores/Investigadores:

Alfonso Noriega Ponce (Facultad de Ingeniería, Universidad Autonoma de Querétaro)
Francisco G Vázquez Cuevas (Instituto de Neurobiología, UNAM)
Vicente Parra-Vega (Robótica y Manufactura Avanzada, CINVESTAV Saltillo)
Rogelio Alcántara Silva (Facultad de Ingeniería, UNAM)
Jose de Jesus Esquivel (Departamento de Matemáticas Aplicadas, IPICYT)
Juan Gonzalo Barajas (Departamento de Matemáticas Aplicadas, IPICYT)
Cesar Octavio Maldonado Ahumada (Departamento de Matemáticas Aplicadas, IPICYT)
Ruben Vazquez Medina (Centro Mexicano para la Producción más Limpia, IPN)
Omar Jimenez Ramirez (Escuela Superior de Ingeniería Mecánica y Eléctrica Culhuacán, IPN)
Jorge X. Velasco (Instituto de Matemáticas, UNAM)
Jose Antonio Cardenas Valderrama (Instituto Politecnico Nacional)
Elizabeth Santiago del Angc (Instituto de Matemáticas, UNAM)

Estudiantes de doctorado:

Eber Jafet Avila Martinez (Departamento de Matemáticas Aplicadas, IPCYT)
Alejandra del Carmen Areola Delgado (Departamento de Matemáticas Aplicadas, IPICYT)
Josue Lobsang Pichardo Mendez (Departamento de Matemáticas Aplicadas, IPICYT)
Oscar Javier Suarez Sierra (CINVESTAV Guadalajara)
Gerardo Navarro Guerrero (Facultad de Ingeniería, UNAM)
Carolina Castañeda (Instituto de Neurobiologia, UNAM Juriquilla)
Mario Alan Quiroz Juarez (Escuela Superior de Ingeniería Mecánica y Eléctrica Culhuacán, IPN)

Estudiantes de Maestria:

Stalin Muñoz Gutiérrez (Universidad Autónoma de la Ciudad de México)
Arturo Franco Lopez (Departamento de Matemáticas Aplicadas, IPICYT)
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Carlos Aguilar Torres (Escuela Superior de Ingeniería Mecánica y Eléctrica Culhuacán,IPN)

Estudiantes de Licenciatura:

Laura Rosina (Licenciatura en Ciencias Agrogenomicas, UNAM ENES Leon)
María Eva Cruz Díaz (Universidad Abierta y a Distancia de México)
María Guadalupe Trejo Arellano (Licenciatura en Tecnologia, CFATA UNAM Juriquilla)

Participantes con adscripción desconocida

Jose Antonio Ramirez Rafael
Rodrigo Brito Interiana
Juan Carlo Puana