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Invited Speakers

Abstracts

Mechanisms of tissue regeneration in the axolotl

Osvaldo Chara

In striking contrast with mammals, many other species have the ability to regenerate substantial parts of their body after tissue amputation. Among the vertebrates, the axolotl (Ambystoma mexicanum), as its most spectacular feature, is able to regenerate the limb and the spinal cord, among other body parts. By means a combination of imaging, cell tracking and mathematical modeling we identified the cellular mechanisms launching spinal cord and limb regeneration in the axolotl. In this talk I will show recent results from our lab suggesting that regeneration triggers a program that seems to mirror development. Moreover I will show preliminary modeling results aimed to ultimately unveil signaling processes triggering the cellular mechanisms resulting in tissue regeneration.

How much does a cell know about its environment?

J.M Pedraza

Cells have different possible phenotypic states, and for a given state of the environment there is a particular phenotypic state that maximizes fitness. A cell would therefore benefit from knowing the environment and adjusting its state accordingly, but this is limited by the noise in gene circuits, imperfect measurements, and the cost of measurement, as well as the limitations on the speed of the state changes. It is possible to quantify the amount of information a cell has about its environment, though this task is complicated if we take into account that environments fluctuate. For a simple system we show, using a combination of simulations and analytical approaches, that cells integrate the past signals with a discount function to determine their future state. Furthermore, a population of cells can have more information about the environment than the population size times the information of an individual cell.

Evolution of drug resistance in fluctuating environments.

Ayari Fuentes

Our understanding of the evolutionary forces driving the adaptation of antibiotic resistant bacteria is mostly based on the assumption of constant, homogeneous environments. In this talk we will focus on discussing how an environment with a heterogeneous temporal structure imposes a dynamic range of selective pressures that can influence the emergence and stability of drug resistance in microbial microcosms. To achieve this goal, we will use data-driven mathematical and computational models combined with single-cell microfluidics and experimental evolution to study how bacterial populations adapt to unpredictable and hostile environments.

Validation and limits of image analysis in cell biology

Matheus Viana

Image analysis is without question the major venue used by biologists to extract meaningful information out of imaging experiments. However, many techniques are used careless, violating fundamental suppositions required to their applicability to particular experiment conditions or types of data. In addition, not much is discussed about the validation of new techniques that are ofter introduced in the literature. In this talk I will discuss my personal experience developing MitoGraph, a software used for quantifying mitochondrial networks in live yeast cells. I will show how we validate MitoGraph and how we evaluate its performance and limitations.

Calcium dynamics in the sarcoplasmic reticulum of smooth muscle cells

Moisés Santillán

Recent experiments, in which calcium release from the sarcoplasmic reticulum of smooth muscle cells is induced with caffeine, apparently contradict the principle of mass conservation. We tackle this problem via a mathematical modeling approach. By introducing a novel scheme of chemical reactions to account for the interaction between calcium and the sarcoplasmic reticulum protein calsequestrin, not only we are able to reproduce calcium binding experiments, but can offer as well an explanation to the above referred apparent paradox. The physiological implications of these findings are finally discussed.

Towards a Large-Scale Comparative Systems Biology across Bacteria: Abasy Atlas, Fractality and Organizational Landscape of Regulatory Networks

Julio Freyre

The availability of databases electronically encoding curated regulatory networks, in addition to high-throughput technologies and methods to discover regulatory interactions, provides an invaluable source of data to understand the principles underpinning the organization and evolution of these networks responsible for cellular control. Nevertheless, data on these sources never goes beyond the regulon level despite the fact that regulatory networks are complex hierarchical-modular structures still challenging our understanding. This brings the necessity for an inventory of systems across a large range of organisms, a key step to rendering feasible comparative systems biology approaches. We take the first step towards a global understanding of the regulatory networks organization by making a cartography of the functional architectures of diverse bacteria. As a result, Abasy (Across-bacteria systems) Atlas (http://abasy.ccg.unam.mx) provides a comprehensive inventory of annotated functional systems, global network properties and systems-level elements (global regulators, modular genes shaping functional systems, basal machinery genes and intermodular genes) predicted by the natural decomposition approach for reconstructed and meta-curated regulatory networks across a large range of bacteria, including pathogenically and biotechnologically relevant organisms. Currently, Abasy Atlas contains systems and system-level elements for 52 regulatory networks comprising 84,956 regulatory interactions covering 42 bacteria in nine taxa, containing 3,887 regulons and 1,891 systems. All this brings together a large body of data that will surely inspire large-scale comparative systems biology studies to generate hypothesis regarding the common principles and particular lifestyle adaptions governing the evolution and organization of systems and their functional architectures across bacteria. In this talk, I will discuss the construction of Abasy Atlas and the results from the first analysis of the available data, including the robustness of the systems-level predictions and the ubiquity of the diamond-shaped architecture, the fractal nature of bacterial regulatory networks and, if time allows, some ideas towards an exploration of their organization landscape.

How mathematical modeling and computer simulation offered the best clue to solve the riddle of polarized growth in fungal cells.

Salomón Bartnicki

The phenomenal growth of fungi is due to their ability to grow tubular cells (hypha pl. hyphae) by rapidly extending the tube at the tip (apex). Apical growth is one the best examples of polarized growth. The search for discovering the secret of apical growth has been pursued since 1892. Elucidation, albeit incomplete, of the mechanism of apical growth has an interesting chronology and is an example of Systems Biology defined by some as "The computational and mathematical modeling of complex biological systems". The first clue to this mystery came in 1924 with the discovery of the Spitzenkörper, a stained spheroidal structure in the apical region of hyphae. Much later (1969), it was discovered that the Spitzenkörper consisted of a collection of secretory vesicles presumed to be responsible for the synthesis of the wall at the apex. But why does the fungus group the vesicles into a single organelle? In the absence of experimental evidence to answer this question, an unrelated study on the mathematics of hyphal growth supplied a likely explanation. Thus in 1989, a computer simulation of the secretory process, with wall-building Vesicles (simulated by pixels) emanating from a Supply Center or VSC, revealed that shape could be controlled by simply moving the VSC! A linear displacement of the VSC yielded shapes almost identical to those of living hyphae. Analyzed mathematically, the process gave the equation $y = x \cot (V x/ N)$ where V is the rate of linear displacement of the VSC and N the amount of vesicles released per unit time. Plotted on Cartesian coordinates, the equation produces a curve, the hyphoid, whose shape is identical to the profile of normal hyphae. Most revealing was finding that the position of the VSC in the hyphoid is the same as the position of the center of the Spitzenkörper in real hyphae. We could therefore predict with near certainty that the function of this organelle is to control shape and direction of growth by serving as a VSC, a concept that has gained wide acceptance among fungal biologists.

Systems Biology to Dissect Nitrogen Responses in *Arabidopsis thaliana.*

Rodrigo Gutierrez

In order to maximize crop yields, agricultural practices worldwide use excess N fertilizers, which have a detrimental impact on the environment and human health. Understanding how plants sense and respond to changes in nitrogen (N) availability is the first step towards developing strategies for biotechnological applications to improve nitrogen-use efficiency. Plants can adjust their capacity to acquire different forms of N in a range of concentrations by modulating the expression and function of genes. Modulation of plant growth and development, most notoriously changes in root system architecture, can also greatly impact plant N acquisition in soils. Using next generation sequencing, integrative network bioinformatics and systems biology approaches in *Arabidopsis thaliana,* we are dissecting regulatory networks acting at different levels to control N-acquisition. At the transcriptional level, genome-wide mapping of DNase I hypersensitive sites (DHSs) and genomic footprinting allowed us to identify regulatory elements controlling gene expression in response to NO_3^-. We delineate *in vivo* transcription factor (TF) binding in the promoter of transcriptionally regulated genes by NO_3^-. Integrated analyses of the data generated lead us to discover NO_3^- sensitive elements and map key TF regulatory interactions underlying transcriptional NO_3^- responses. Our genomic strategy identified new candidate TFs as well as positioned the contribution of known regulatory factors in the transcriptional network mediating changes of gene expression in response to NO_3^-. We will also discuss advances towards mapping these gene networks to developmental responses for optimal N nutrition in *Arabidopsis thaliana*. Our results offer important new targets for biotechnological strategies to improve crop production in economically and environmentally sustainable ways.

Epithelial folds, cell proliferation, and the control of organ size during development

Marcos Nahmad

During development, cells communicate with each other to coordinate patterning, growth, and morphogenesis. One form of communication is through cell-cell interactions exerted by physical forces. However, it is little clear how cells interpret mechanical interactions and how these affect cell functions. In the Drosophila wing imaginal disc, the larval tissue that develops into the adult wing, mechanical interactions among cells influence their ability to grow and proliferate; cells that compress each other proliferate poorly, while cells that interact with each other loosely proliferate faster. Conversely, when a cell in the disc grows and divides, it alters the distributions of physical forces among its neighboring cells resulting in feedback between cell proliferation and mechanical interactions. These observations together with mathematical modeling studies have proposed mechanical feedback as a mechanism for growth control in the wing disc; however, these studies assume that the disc is a flat 2D-array of cells and ignore deep folds that form within the disc and may alter mechanical interactions among the cells. In this project, we investigated the correlation between fold formation and global patterns of cell proliferation in the wing disc. We developed image-processing tools to quantify how cell proliferation changes as a function of distance to the fold. We found that cell proliferation is significantly higher next to the folds, consistent with our hypothesis that the epithelial folds release cell-cell tension locally that may favor higher proliferation. Using Drosophila genetic tools, we attempted to eliminate the epithelial folds, but were unable to do so, suggesting that fold formation is a robust developmental process. In order to determine if the correlation between fold formation and cell proliferation is a causal relationship, we genetically generated ectopic folds in fixed and live wing discs and quantified the cell proliferation patterns around the ectopic fold. We present evidence that folds affect cell proliferation, perhaps playing a key role in determining final size and shape.

Robustness, control and the organization of developmental pattern

Arthur D. Lander

Tissue-scale pattern formation depends upon the ability of cells to make decisions based on their locations. They do this, at least in part, by obtaining cues from signaling molecules known as morphogens, that are distributed in long-range spatial gradients. The molecular machinery required to make and respond to morphogen gradients is relatively simple, whereas the machinery that developing organisms actually employ is remarkably complex, typically involving layers of regulation through feedback-controlled uptake, secreted inhibitors, transport modulators, co-receptors, expanders, etc. In my talk, I will seek to connect the complexity of such machinery to the systems-level engineering objectives of robustness and control. Drawing upon experiments and mathematical models of pattern formation in fruitfly wings, I will illustrate some of the ways in which mechanistic complexity is driven by tradeoffs among strategies for dealing with real-world disturbances.

Modelling the complex regulatory interplay between Epithelial-Mesenchymal-Transitions and the Microenvironment to understand and predict the oncogenic progression of liver cancer

Elisa Domínguez-Hüttinger

Epithelium to mesenchymal transition (EMT) is a complex cellular trans-differentiation process through which epithelial cells acquire a mesenchymal phenotype with the ability to invade other tissues. Under homeostatic conditions, EMT participates in wound healing, development and organogenesis. However, EMT is also involved in the tissue remodelling that characterizes pathological chronic degenerative processes, such as fibrosis and carcinomas, accounting for 51% of deaths worldwide. It remains to be investigated how EMT-driven tissue remodelling, needed for the maintenance of tissue homeostasis, becomes aberrant and a driving force of pathologies such as cancer and fibrosis. The EMT is controlled by the complex interactions betweenTranscription Factors, operating within individual cells in the tissue, and changes in the surrounding micro-environment, given by the composition of the extracellular matrix (determining tissue stiffness), and the levels of pro-inflammatory cytokines such as TGF. In turn, the mesenchymal cells produce ECM components and cytokines, forming a positive feedback loop between the phenotypes of the cells and the properties of the surrounding tissue. While in equilibrium this complex feedback control structure preserves homoeostasis, we hypothesized that perturbations of this system by genetic or environmental risk factors known to predispose to fibrotic or oncogenic conditions, the equilibrium between positive and negative feedback loops is impaired, which can lead to the onset and progression of pathology. Here, we use a systems biology approach and represent this complex multi-scale feedback control structure with a mathematical model. Using control theoretical approaches, we analyse this model to identify the different perturbations that can drive aberrant tissue remodelling processes, identifying the different risk factor combinations that drive the transition from a homoeostatic to pathological tissue repair process in hepatocytes. We could also quantitatively characterize the different micro-environmental signals, in terms of the minimal input amplitudes and frequencies required to break the stability of the system and, forcing the transition from an epithelial to a mesenchymal state. Simulations of our multi-scale model show that an increased strength of in the positive feedback loop between the phenotypic decision-taking and the microenvironment cues can lead to an abrupt transition from a homeostatic to a pathological tissue with an over-accumulation of mesenchymal cells. Our analysis demonstrates how a system biology approach for the identification of underlying mechanisms in the onset and progression of complex diseases.

Feedback control of mammalian cell differentiation

Mary N. Teruel

Mammalian tissue size is maintained by slow replacement of de-differentiating and dying cells. For adipocytes, key regulators of glucose and lipid metabolism, the renewal rate is only 10% per year. We used computational modeling, quantitative mass spectrometry, and single-cell microscopy to show that cell-to-cell variability, or noise, in protein abundance acts within a network of more than six positive feedbacks to permit pre-adipocytes to differentiate at very low rates. This reconciles two fundamental opposing requirements: high cell-to-cell signal variability so that differentiation rates can be kept very low and low signal variability to prevent differentiated cells from de-differentiating. Higher eukaryotes can thus control low rates of near irreversible cell fate decisions through a balancing act between noise and ultra-high feedback connectivity.

We have gone on to explore the nature of the adipocyte differentiation network architecture in the physiological context and have found, intriguingly, that a circadian signaling code restricts the rate of cell differentiation. Dysregulation of the circadian pattern of glucocorticoid oscillations by irregular feeding and sleep cycles, by long-term hormone treatment, or during metabolic diseases, have all been shown to cause obesity. Here we use live single cell analysis to determine if and how oscillatory hormone pulse patterns control the rate of adipogenesis to explain the observed increase in fat mass. Strikingly, by monitoring endogenously-tagged PPARG, CEBPB, and FABP4 during the differentiation process, we show that adipocyte precursor cells reject circadian hormone pulse patterns but not continuous ones. We identify a network that combines fast and slow positive feedback loops as a unique regulatory motif that selectively suppresses differentiation for circadian pulse patterns. Together, our study provides a molecular mechanism for why stress, Cushing's disease, and other conditions for which glucocorticoid secretion loses its pulsatility can lead to obesity.