Variability in Biology

Systems Biology Program Workshop, CNB-CSIC, May 30 2022, Madrid, Spain
(Registration for attendance is required. Please contact Juan F Poyatos jpoyatos at cnb.csic.es
Zoom link: https://rediris.zoom.us/j/84195337524 Meeting ID: 841 9533 7524)

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9 – 9.30
Welcome

9.30 – 10.00
Ard A. Louis
Symmetry and simplicity spontaneously emerge from the algorithmic nature of evolution

10.15 – 10.45
Aurora Gómez-Durán
Mitochondrial DNA variation and stress responses

11.00 – 11.30
Coffee Break

11.30 – 12.00
Juan F. Poyatos
The interpretability of phenotypic predictions from genetic variation

12.15 – 12.45
Santhosh Girirajan
Dissecting the variability in complex neurodevelopmental systems

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1.00 pm – 3.00 pm
Lunch

3.00 – 3.30
Saúl Ares
Feedback control of eye size variability in *Drosophila*

3.45 – 4.15
Luciano Marcon
Order form disorder: The role of Turing network topology in noise canalization and pattern formation

4.30 – 5.00
Coffe Break

5.00 – 5.30
Jaime de La Rocha
Harnessing behavioral variability during perceptual decisions.

5.45 – 6.15
María Figueres-Oñate
Brain heterogeneity decoded by lineage tracing

6.30 –
Final discussion.
How should we progress on all these problems?

What are the speakers going to talk about?

Ard A. Louis

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Engineers routinely design systems to be modular and symmetric in order to increase robustness to perturbations and to facilitate alterations at a later date. Biological structures also frequently exhibit modularity and symmetry, but the origin of such trends is much less well understood. It can be tempting to assume—by analogy to engineering design—that symmetry and modularity arise from natural selection. However, evolution, unlike engineers, cannot plan ahead, and so these traits must also afford some immediate selective advantage which is hard to reconcile with the breadth of systems where symmetry is observed. Here we introduce an alternative nonadaptive hypothesis based on an algorithmic picture of evolution. It suggests that symmetric structures preferentially arise not just due to natural selection but also because they require less specific information to encode and are therefore much more likely to appear as phenotypic variation through random mutations. Arguments

from algorithmic information theory can formalize this intuition, leading to the prediction that many genotype–phenotype maps are exponentially biased toward phenotypes with low descriptional complexity. A preference for symmetry is a special case of this bias toward compressible descriptions. We test these predictions with extensive biological data, showing that protein complexes, RNA secondary structures, and a model gene regulatory network all exhibit the expected exponential bias toward simpler (and more symmetric) phenotypes. Lower descriptional complexity also correlates with higher mutational robustness, which may aid the evolution of complex modular assemblies of multiple components.

Aurora Gómez-Durán

biological research centre margarita salas

https://www.cib.csic.es/research/molecular-biomedicine/mitophenomics

Mitochondrial DNA (mtDNA) variants influence the risk of rare and late-onset human diseases, but the reasons for this are poorly understood. Interestingly, the same variant exerts a great variability in disease penetrance in each individual, which suggests the existence of a complex system that does not necessarily imply the dysfunction of the energy synthesis. In here, through the combination of multi-omics approaches on several human models, we will describe how variations in oxidative phosphorylation system capacity (OXPHOS) driven by the mtDNA variants activate different types of stress responses and their possible role in late-onset disease. We will further show how these findings can be applied to pharmacogenomic discovery and search of new biomarkers.

Juan F Poyatos

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Perhaps one of the most essential questions in biology is how we can predict phenotypes. Quantitative genetics has taught us that for this purpose we can use existing genetic variation and interpret this resource as a multifactorial perturbation that helps us infer associations between the genotype and the phenotype. How these associations are generated is however something we do not usually know. That is, we face limits in the interpretability of our predictions. In this talk, I will present our latest efforts to advance in this interpretability. We will use what is perhaps the best computational model of current systems biology, the genomic-wide metabolic models, and consider cell growth as the focus phenotype. We are going to open the "black box" of metabolism to understand which factors determine growth prediction and their relationships with the architecture of the system and the interactions with the environment. Predicting is difficult but we should try to understand why.

Santhosh Girirajan

Pennsylvania State University
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Recent studies have identified different classes of genetic variants that vary in effect size and population frequency towards complex disorders such as autism and intellectual disability. These studies have identified several challenges in our understanding of the functional basis of these disorders. *First*, most gene discoveries for these neurodevelopmental disorders rely on identifying *de novo* mutations. In fact, only less than 25% of cases of complex disorders could be attributed to *de novo* mutations in single genes. *Second*, the same variant or gene has been associated with different clinical outcomes, such as the 16p11.2 deletion associated with both autism and epilepsy. *Third*, incomplete penetrance and variable expressivity have a complicated clinical diagnosis and genetic counseling. My laboratory uses a combination of human genetics, model systems, and computational approaches to untangle the complexity of genetic disorders. We will present our findings on studying quantitative traits in thousands of genetic interactions of conserved neurodevelopmental genes using *Drosophila melanogaster* and *Xenopus laevis* models, clinical measures from hundreds of human families affected with intellectual disability and autism, and novel statistical approaches for identifying relationships between variants, genes, and genetic pathways to specific phenotypes. A systems level approach has allowed us to dissect variability of traits and disease phenotypes, and to identify diagnostically relevant genetic etiology for complex disorders. We believe these and future efforts in this direction can potentially identify the missing heritability of complex disorders.

Saúl Ares

national biotechnology centre
http://www.cnb.csic.es/index.php/es/component/k2/item/1548-clocks-and-rulers-in-life

The size of some organs is remarkably precise. Most organs are specified as small primordia whose growth is exponential. However, exponential growth is prone to amplify the noise that is inescapable to biological processes. This fact has led to the proposal that organ development must be subject to mechanisms of feedback control which, in the engineering sense, reduce their internal “developmental instability”, increasing the precision with which organs reach their species-specific size. Some organs that undergo constant tissue renewal, like the olfactory epithelium, maintain their size homeostasis through an integral feedback. Some other organs, though, grow to a size that, once reached, cannot be further modulated. This is the case of insects. After their last molt, the adult organs are covered in a rigid chitin exoskeleton that precludes further size regulation. The eye of fruit flies serves as a good example of organ growth: In *Drosophila*, the end point of eye development is reached when all retinal progenitor cells differentiate, as differentiation is accompanied by the exit of the cell cycle. Two features should have resulted in a strong evolutionary pressure to maximize the precision in eye size: on the one hand, left and right eyes must survey a symmetrical part

of space; on the other, making and maintaining the eyes is energetically very expensive. To investigate the mechanism by which the Drosophila eye ensures its size precision, we downregulated the expression of *dpp*, a morphogen produced by newly differentiated retinal cells. This had two effects: reduction of the eye size, and a dramatic increase in the disparity of sizes between both eyes of each fly. Under *dpp* downregulation apoptosis was increased in the eye progenitors: inhibiting apoptosis rescued the phenotype. Using a simple stochastic model of eye development, we found that the noise in apoptosis is the key to the variability in eye size upon *dpp* downregulation, and that Dpp mediates a feedback control mechanism that contributes to the precision in eye size.

Luciano Marcon

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Turing gene regulatory networks are prominent models to study multi-cellular self-organization but it is still unclear how they can drive different self-organizing behaviors. Here we use an automated algebraic method to derive a topological atlas of self-organizing Turing networks that can generate periodic patterns, traveling waves or noisy amplifying patterns. The atlas reveals that different self-organizing behaviors are grouped into distinct topological clusters that are characterized by specific network feedbacks. These clusters are connected together by multi-functional networks that can transition between self-organizing behaviors upon feedback modulations. These transitions can explain changes in patterning dynamics such as the progression from axis formation into somitogenesis that is observed during early embryonic development. Our analysis also reveals that feedbacks on cell-autonomous nodes play a central role in canalizing the noise of the system by controlling the speed and precision of pattern formation. Taken together, our results show that changes in network topology and feedback modulations can drive continuous transitions between Turing behaviors, providing a novel framework to study the evolution and development of multi-cellular self-organization.

Jaime de la Rocha

Idibaps
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Perceptual decision making has become a canonical paradigm in cognitive psychology and more recently in systems neuroscience. Perceptual decisions based on ambiguous evidence can be strongly variable, a property which has been classically linked to variability in neural activity. But perceptual decisions do not only reflect current sensory information but are also shaped by recent experience. The mechanisms underlying these history-dependent decision variables remain however largely unexplored. In this talk, I will show a novel auditory discrimination task done in rats, in which we varied the statistics of the stimulus sequence in order to probe the animal's ability to predict upcoming stimuli. Rats adapted to this

environment and developed a strategy that capitalized on the serial correlations of the stimulus sequence they generalized the common action-based reinforcement learning (RL) to a rule-based RL strategy. To assess the role of different brain areas in the encoding of the rule value, we used optogenetics to inhibit neural activity during the task. We found that inactivation of the pre-frontal cortex and the striatum decreased the impact of the rule value on the immediately subsequent choice while sparing the processing of the stimulus. Finally, we performed neural recordings in the striatum during the task and found that a significant fraction of neurons encoded the trial-by-trial variations in rule value. Our results suggest that, during perceptual decisions, reinforcement learning of rules and actions dependent on the cortico-striatal pathway, is an important factor guiding animals' choices.

María Figueres-Oñate

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During development, a pool of neural progenitors proliferates and differentiates until the adult brain reaches an appropriate size and cellular composition. One of the most challenging questions in Developmental Neurobiology is to understand how this complex process takes place. Every single progenitor generates not only a concrete number of sibling cells but also different cell types that are accurately distributed to form complex brain networks. Progenies derived from scattered progenitors at neurogenic niches are generated within a specific embryonic temporal pattern. Clones from different developmental origins will come together to form the functional adult nervous system. In this context, lineage cell tracing appears as a sophisticated and challenging process that aims to reconstruct the offspring arising from a single progenitor cell. Thus, to further investigate how the brain network is built, we use a multicolor clonal method to trace lineages from single neural progenitors, named UbC-StarTrack. The ubiquity of the employed tool allowed us to track cells with distinct fates from neural progenitors at different time points and from diverse brain areas, such as the cerebral cortex, olfactory bulb, the thalamus, or the cerebellum. Decoding clonal relations in the adult brain may lead us to a better understanding of the broad heterogeneity within adult cell populations.