Jacques Loeb Centre
for the History and Philosophy
of the Life Sciences
Prof. Ute Deichmann, Director

Ben-Gurion University of the Negev
P. O. Box 653, Beer-Sheva, 8410501, Israel
Building 39, Room-112 | Phone: +972-8-6472258
Email: jloebcentre@post.bgu.ac.il | Web: in.bgu.ac.il/en/loeb

# Abstracts

## Workshop 'Plasticity and Constancy in Development and Evolution', Ben-Gurion University of the Negev, May 9-10, 2022

### Proteins that interpret genomic signals to stabilize cell identity

Adrian Bird, University of Edinburgh, U.K.

The identity of differentiated cell types is remarkably stable. This lecture will explore two ways in which this is achieved via proteins that interpret genomic signals to stabilize and optimize gene expression programs. Evidence will be presented that the chromatin protein MeCP2 interprets the local DNA methylation density to modulate gene expression levels in the mature brain. Loss of MeCP2 by mutation compromises neuronal function, leading to the neurological disorder Rett syndrome. A second signal that affects gene activity globally is DNA base composition. We found that the protein SALL4, which stabilizes the embryonic stem cell state, depends for its function on binding to short AT-rich DNA sequence motifs whose frequency fluctuates dependent on base composition. Loss of this protein as cells differentiate normally appears to facilitate the differentiation process by allowing up-regulation of differentiation genes.

### Genomic view of gene regulatory elements and their role in human disease

Ramon Birnbaum, Ben-Gurion University of the Negev, Israel

As less than 2% of our genome codes for proteins, the majority of our genome (>98%) encompasses important sequences that function as gene regulatory elements, instructing genes when, where and at what levels to turn ON or OFF.

Increasing evidences suggest that non-coding variation is a significant risk factor for human disease, but how these variants contribute to the phenotype remain elusive. In my talk, I will focus on distal transcription enhancers that promote gene expression, enabling spatiotemporal control of genetic programs such as those required in developmental processes. I will describe how to identify and functionally characterize enhancers and I will describe several examples of how mutations in these elements have been found to cause human disease. As the sequencing technologies tremendously improved, our ability to identify disease-associated mutations in these regulatory elements is rapidly increasing. Thus, deciphering the regulatory code is necessary to accelerate our basic knowledge about the human genome and diseases.

## About time: The dynamics of nervous system development

James Briscoe, Francis Crick Institute London, U.K.

The embryonic development of tissues is a dynamic process coordinated by intercellular signalling that direct gene regulatory networks to assign cell fate. At the same time tissue growth and differentiation alters the arrangement and number of cells, contributing to the elaboration of pattern. Together these mechanisms determine the pattern, pace, precision, and proportion of forming organs. Thus, accurate development and the specification of specialised cell types relies on the interplay of cellular and molecular processes. To understand this, quantitative approaches together with predictive and dynamical models are needed that allow the analysis of cellular differentiation dynamics and offer insight into the principles of tissue development.

## Serial homology and segmental identities in arthropod development and evolution

Ariel D. Chipman, The Hebrew University of Jerusalem, Israel

The arthropod body is composed of a series of units along the anterior-posterior axis of the body, known as segments. These segments are generally considered to be evolutionary repeats of similar units, or in other words, serially homologous. However, despite the common evolutionary history and the many similarities among the segments, they are different from one another, and these differences

are highly plastic across the diversity of arthropods. What can we learn about the evolutionary history of different segment “types” from their development? At what point in development do segments adopt a distinct identity? Are all segments indeed serially homologous? What level of difference justifies referring to segments as non-homologous?

## The idea of constancy in development and evolution - scientific and philosophical perspectives

Ute Deichmann, Ben-Gurion University of the Negev, Israel

First, I argue that the notions of stability and constancy of species that emerged in the 18th century against the background of widespread assumptions of their plasticity and transmutations was a prerequisite for the systematic study of non-stochastic, ordered species change, i.e. evolutionary biology, as expressed by Michel Morange (2021), "The theory of evolution had no place in a world where the existence of monstrous hybrids was accepted or where the most fantastical transformations were conceivable."

This leads to the question of how constancy or stability in nature can be maintained in view of ubiquitous random processes? On the one hand, these processes are at the basis of life, because thermal molecular movements enable biochemical reactions in the cell and lead to the diversity of organisms in evolution. Random mutations have also led to biological specificity and the individuality of organisms. On the other hand, random processes, such as fluctuations of important molecules or chromosomal rearrangements increase stochasticity and prevent deterministic outcomes.

I show that constancy in nature is associated with organisms' structural and organizational hierarchies, particularly the hierarchy of gene-regulatory networks, and genetic causality, which are fundamental principles of life. Physical-chemical models that marginalize hierarchical organization and the central role of genes in development cannot convincingly account for the observed constancy in development and evolution. However, an integration of physical-chemical processes such as reaction diffusion mechanisms and genome-based mechanisms of form generation has recently proved fruitful in explaining the development of some periodic structures.

The tension between change and constancy was also a topic in ancient Greek philosophy. I claim that the idea of change in development and evolution being based on constancy, i.e. the reliable transmission of genomes over long periods of time has a historical parallel in the ancient atomists' attempts to explain

change through movements and interactions of unchangeable entities, the atoms.

## A molecular analysis of constancy and flexibility during vertebrate development

Denis Duboule and Colleagues

Ecole Polytechnique Fédérale, Lausanne, Switzerland

Collège de France, Paris, France

University of Geneva, Switzerland

As initially observed by Ernst Haeckel, vertebrate embryos tend to maximally resemble one another during a short time-period of time, precisely when embryos start to get organized to reach the form of a ‘foetus’ or of a ‘larva’. This period can last from a few hours to a few days, depending of the species, and is referred to as the phylotypic progression (Slack et al., 1993; Duboule, 1994), since all embryos, during this time-period, express the same set of conserved genes and seem to implement highly conserved mechanisms thus defining a ‘phylotype’ i.e., an archetype of all animals belonging to the vertebrate taxon. Before and after this particular developmental period, forms can be more variable due to adaptation to environmental conditions (in water, in an egg, in a uterus..) thus leading to the concept of the ‘developmental hourglass’ proposed in 1994.

The variety of forms observed at very early stages (higher plasticity leading to a wider morphospace) thus ‘converge’ (Keibel, 1906) towards this particular developmental interval (the neck of the hourglass), as if an evolutionary constraint would prevent (restrict) developmental flexibility at this point. In 1875, Wilhelm His already formulated the question as to what would cause this convergence and several explanations were proposed ever since the developmental hourglass was formalized in 1994. One such explanation is that two time-devices are meeting at this precise point and must be implemented in full coordination within each species; One the one hand, the segmentation clock, which produces iterated segments due to mechanisms acting in trans and, on the other hand, the Hox timer, which will identify each newly produced segments through the time-specific activation of new Hox genes, based on a mechanism acting in-cis (dixit Lewis, 1978). The nature of the latter process has remained elusive ever since its initial observation in 1989, due to the difficulty to approach it using the small and complex early gastrulating mouse embryo as a model system. I will discuss our results using pseudo-embryos (produced out of

embryonic stem cells and referred to as gastruloids) and show some data indicating how this timer does actually work at the molecular level. Interestingly, while the parallel implementation of these two time-devices understandably imposes some strong rules to the general vertebrate body plan (constancy), it also provides a rather simple way to evolve morphologies (plasticity) within a globally comparable blueprint.

## Aristotle vs. Evolutionary Theory: Identifying the Most Difficult Question

Andy German, Ben-Gurion University of the Negev, Israel

Aristotelian scholars and philosophically inclined biologists have long recognized that while Aristotle himself certainly held that biological species are (largely) fixed and eternal, and thus denied the central tenet of evolutionary biology, his basic metaphysical and physical principles can, without violence, be interpreted in such a way as to accommodate a diachronic, evolutionary picture of species relations. It is not here, then, that the theoretical divide between Aristotelian and evolutionary biology is to be found, I argue.

In his De Generatione Animalium, Aristotle says that “the question of greatest difficulty” lying in wait for all accounts biological development is: “Whence, how and when does intellect (nous) come to be present in those animals having a share in this principle?" That is, can the presence of the power of intellect ever be understood as coming-to-be via a process of development (whether random or otherwise)? For Aristotle, the answer will prove to be no. While he has a subtle account of biological life as organized for, and developing toward, the exercise of higher perceptual and ultimately cognitive functions, there is nevertheless a break, or leap. As an investigation of Aristotelian embryology will show, the highest of all cognitive functions – the unmediated grasp of intellectual form – does not result from any diachronic development, no matter how detailed in articulation. This is because intellect always already a kind of being (ousia) when it appears in us. It is never a “coming-to-be”. And yet, says Aristotle, “The activity (energeia) of the intellect is life”.

## Stability and Change: Some Ancient and Modern Perspectives

Edward Halper, University of Georgia, U.S.A.

Why does an organism sustain itself? Dennett and others have proposed that organisms evolved to do so. This paper argues, first, that evolution cannot explain an organism's striving to persist because it presupposes that striving. More broadly, the paper contends, secondly, that the scientific paradigm introduced in the modern period (17th century) is equally unable to account for the organism's persistence. According to this paradigm, events are caused by bodies, forces, charges, or whatever that act necessarily and produce necessary effects. To apply the paradigm to an organism requires (1) treating the organism as a machine, thereby undermining its potential for adaptation (and contradicting evolution, I think) and (2) explaining the functioning of the whole by means of a part. Third, the Aristotelian approach to science, the paradigm that modern science displaced, directly addresses the question of why organisms sustain themselves and, and, indeed, takes the functions and processes that an organism performs to sustain itself as its essential nature. Hence, this approach amounts to a kind of inversion of modern science: the processes are sources of stability and material is the source of plasticity. The paper raises the question whether some such ontological transformation has taken place in Davidson's approach to regulatory networks.

## Boundaries of Change and Development in ancient atomistic theory

Philippa Lang, Emory University, U.S.A.

Questions of how to account for change, and what could be defined as everlasting, were preoccupations of ancient Greek philosophy, from the generations before Socrates to the Roman empire. This paper focuses on how the need to explain both constancy and variation drove the invention and refinement of the ancient 'atomist' theory of matter and summarises the essential features of the theory, concentrating on how change and variety exist in tension with the material permanence of the unbreakable atoms themselves. It then focuses on the Latin philosophical poem On the nature of things to inquire into the limits of such variation. I will argue that as complex and co-determined atomic entanglements emerge from initially random conditions, the possibility paths for how that world develops become increasingly narrow, especially in relation to animals, humans, and human society. The evolution of regularity and continuity,

such as that visible in repeated generations of a single species, is consequently an inevitable feature of random atomic motion in the infinite void; even though atomist theory also guarantees that every such emergence of order is temporary.

## Cell type evolution and the emergence of organ function

Joseph Parker, California Institute of Technology, Pasadena, U.S.A.

How do cell types evolve to cooperate with each other, generating organ-level behaviors? Animal organs are composed of distinct cell types that act collectively, producing emergent biological functions. Yet, how this cooperativity arises during evolution via molecular changes in individual cell types remains poorly understood. To answer this question, we retraced the functional co-evolution of cell types comprising a beetle chemical defense gland. We find that the gland is composed of two cell types that collaborate to make a chemical cocktail that is greater than the sum of its parts. By inferring how each cell type gained its function, we employed a set of experimental approaches that enabled us to connect these specific molecular evolutionary steps to adaptive changes at the organismal level that are only realized when the two cell types work in concert. Based on our findings, we propose a general model for the evolution of codependence between cell types—one that can be extended to explain the emergence of cooperation between diverse cell types in more complex organs.

## Continuities between adaptive and innate immune-cell developmental programs: a clue to evolutionary history?

Ellen V. Rothenberg, Division of Biology and Biological Engineering, California Institute of Technology, Pasadena, U.S.A.

Vertebrate blood cell development, hematopoiesis, is a distinctive developmental system in which cell fate and cell function are established and maintained through mechanisms mostly working at the single-cell level. That is, cells determine what they will become without reference to positional information, morphogen gradients, or coordinated tissue folding or stretching movements. Hematopoiesis generates blood cells that specialize in gas exchange (red blood cells), clotting to heal damaged vasculature (platelets or thrombocytes), and a

very diverse array of immune and inflammatory cell types (macrophages, neutrophils, mast cells, dendritic cells), along with a separate reservoir of stem and multipotential progenitor cells that temporarily proliferate while delaying differentiation to any of the effector types. All of these cell types have distinctive gene expression programs directed by different combinations of transcription factors. Some of the transcription factors and circuit elements that specify these cell types have roots that go far back in evolutionary time, to non-vertebrate deuterostomes and protostomes. Blood development thus confronts us with a challenge: does our knowledge of gene regulation at the single-cell level really go far enough to explain how these different cell types arise?

The problem this talk will address is the origin of another type of immune cell, adaptive immune cells (B and T lymphocytes), which are only seen in vertebrates. These two major lineages of cells add one more element to the establishment of their identities. They undergo a programmed DNA rearrangement with a high error rate as an integral part of their differentiation. Then, their survival is made to depend on the outcome of this DNA rearrangement. Both the error-prone DNA rearrangement and the harsh selection for rearrangement success are alien to the developmental programs of the other hematopoietic cells. Even for cells that acquire the machinery for the gene rearrangement process, how could the developmental pathway itself have been adapted to make such a high-risk process useful and effective? Recent molecular evidence indicates specific gene regulatory program modules that give the cells the ability to undergo selection like this. The talk will focus on the way the “selection modules” relate to the separate gene network modules controlling the progenitor and effector identity gene regulation programs. The network relationships seen suggest that a network unit controlling recombination as well as selection can act as an optional and tunable “plug-in” for the developmental process of these cells, enabling a range of diverse cell behaviors to emerge.

## Causality in developmental disorders

Stanislav Shvartsman, Princeton University, U.S.A.

Germline mutations upregulating Ras signaling are associated with a class of monogenic developmental disorders. A hallmark of these conditions is that the same mutation may present vastly different phenotypes in different individuals, even in monozygotic twins. Here we demonstrate how the origins of such largely unexplained phenotypic variations may be dissected using highly controlled studies in Drosophila that have been gene-edited to carry activating variants of MEK, a core enzyme in the Ras pathway. The fraction of mutation carriers reaching adulthood was strongly reduced, but most surviving animals have

normal Ras-dependent structures. We rationalize these results using a stochastic signaling model and support it by quantifying cell fate specification errors in bilaterally symmetric larval trachea, a Ras-dependent structure that allows us to isolate the effects of mutations from potential contributions of genetic modifiers and environmental differences. Our findings shed light on phenotypic heterogeneity of developmental disorders caused by deregulated Ras signaling and offer a framework for investigating variable effects of other pathogenic alleles.