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Genomic Regulation: Experiments, Computational Modeling and Philosophy

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Abstracts

(By Author)

Highly conserved developmental program for tube formation downstream of VEGF signaling
Modi Roopin, Smadar Ben-Tabou de-Leon, et al (University of Haifa, Israel)

The vascular endothelial growth factor (VEGF) pathway that in humans stimulates the formation of new blood vessels (angiogenesis) is a critical element in the development of an embryonic skeleton in sea urchins (skeletogenesis). The exact role of VEGF in spicule formation, VEGF target genes and whether there are other similarities between the control of sea urchin skeletogenesis and vertebrates' angiogenesis were largely unknown. Here we study the cellular and molecular machinery activated by the VEGF pathway during sea urchin skeletogenesis and find remarkable similarities to the mechanisms that drive tubulogenesis during vertebrate angiogenesis. We demonstrate that human VEGF is capable of inducing ectopic spicule branching in the sea urchin embryo. We show that VEGF signaling is essential for the construction of a cytoplasmic tube that surrounds the sea urchin spicules. We identify novel VEGF target genes, among them homologs of angiogenic genes. We show that VEGF target rhopag24l/2 and its upstream activator ROCK1, regulate spiculogenesis and spicule branching. Human rhogap24 and ROCK1 regulate vessel formation and branching through cytoskeleton remodeling downstream of VEGF signaling. Thus, VEGF regulation of tube formation through the control of cytoskeleton remodeling machinery may have been the common evolutionary origin of sea urchin spiculogenesis and vertebrate angiogenesis.

Mendel, Michaelis and Davidson: Mathematical methods in the history of biology and their challenge in 'empiricist' big data-driven science

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

Mathematical models have a long history in biology. They were used, among other things, as predictive hypotheses for devising and structuring new experiments or as descriptions and simulations of reality. Using various cases of mathematical modelling in biology, from Mendel's model of heredity in the 19th century to Turing's model of development in the mid-20th century, this paper examines their epistemology and unequal success. Against this historical background I will analyze the impact of big data technology on the epistemology of models in 21st-century experimental systems biology, in particular GRN research, and discuss the future of mathematical modelling in biology.

Changing views of evolutionary novelty: Prospects for a general model

Douglas H. Erwin (Smithsonian National Museum of Natural History, U.S.A.)

Novelty is a topic of broad interest, from evolutionary biologists to anthropologists and economists. Economists and those interested in cultural and technological evolution have frequently borrowed ideas and insights from evolutionary biology as justification for a variety of models of evolutionary novelty and innovation. Within evolutionary biology there have been two distinct approaches to evolutionary novelty, each extending back to the early 19th century. Since Darwin, the dominant approach has been transformationist, with evolutionary novelty arising through gradual changes in morphology. Since the Modern Synthesis of the 1930s-1950s this view has emphasized the importance of ecological opportunity rather than the source of variation. Well before Darwin, however, an alternative view arose which held that novelties could arise by rapid changes. Advocates of this approach have suggested a variety of mechanisms, from the German Idealist morphology, to Lamarkians and orthogenecists. As some of the advocates of such transformationist approaches have been religious or rejected natural selection (and a few have had abhorrent political views) it has been easy for transformationists to caricature their views. The rise of comparative evo-devo since 1990 has led to a resurgence of transformationist arguments, however, and suggestions that it may be possible to develop a general theory of novelty and innovation covering biological, cultural and technological domains. Such a theory could take one of several different forms: 1) A general, formal theory. 2) Commonalities might exist across domains but with sufficient differences between domains that any formal theory would be domain-specific. 3) Commonalities exist across domains but for various reasons developing a formal theory even within domains is improbable. However, a general conceptual framework covering the three domains can be developed while acknowledging some degree of domain specificity. 4) Despite apparent metaphorical similarities across domains, processes of

novelty, invention and innovation are sufficiently specific within different domains (and may vary so much within domains) that even building a domain-specific framework is a hazardous enterprise. Finally, it remains possible that the entire enterprise of seeking a general theory of novelty and innovation is so obviously delusional that anyone pursuing it should be strongly medicated.

Chemical experimentation and biological modeling: The emergence of DNA sequencing and the configuration of the genome as an informational object

Miguel García-Sancho (University of Edinburgh, U.K.)

In this presentation, I will explore the career of Frederick Sanger, the inventor of the first protein and DNA sequencing techniques (1943-1977). I will focus on the transition of Sanger's research interests from protein to nucleic acid sequencing, which culminated with Sanger's professional migration from the Department of Biochemistry of Cambridge to the newly founded MRC Laboratory of Molecular Biology (LMB), in 1962. Shortly after his move, Sanger changed his sequencing strategy and instead of degrading the target molecule into fragments – as he had done to reconstruct the order of amino acids in proteins – he deduced the sequence by intervening in the duplication process of DNA. I will argue that this shift from a degradation to a copying approach was shaped by Sanger's institutional move: at the Biochemistry Department, Sanger's sequencing followed the experimental culture of analytical and synthetic chemistry, while after his arrival to the LMB he gradually modelled his techniques into the mechanism of DNA replication, a main field of interest for molecular biologists in the 1960s.

I will also show how Sanger's DNA sequencing methods changed the way molecular biologists understood genetic information and approached this research object experimentally. Building on the work of philosopher of biology Lenny Moss – who has distinguished between a Gene-P and Gene-D concept – I will argue that before the 1970s genetic information was a set of instructions that DNA transmitted to proteins. Sanger's sequencing techniques provided genetic information with both a molecular entity – an arrangement of nucleotides in the DNA strands – and a means to experimentally tackle that entity. Since the publication of those techniques (1975 to 77), molecular biologists increasingly directed their efforts to the genomes of different organisms and used information technologies as an aid for that endeavor.

Eric Davidson's "Regulatory Genome" for Computer Scientists

Sorin Istrail (Brown University, U.S.A.)

In his book, The Regulatory Genome: Gene Regulatory Networks (GRN) in Development and Evolution (Academic Press 2006), Eric Davidson, the foremost experimentalist of regulatory genomics, forcefully reminds us that in the scientific method, causality is everything; all other

approaches are just distractions. In contrast, Davidson — a notoriously elegant writer — offers devastating criticism of the “posterior Biology” approaches all too impatiently employed today — the “measure first” expression of thousands of genes and then “computationally infer Biology.” The last century’s luminaries of mathematical statistics taught us in no uncertain terms that causality cannot be inferred from statistical tables. Davidson aligns with them, adding to their argument a practical dose of reality. The exquisite regulatory mechanisms, locked down by evolution, can only be revealed through systematic experimental perturbations. Like his mentor Max Delbruck, and with the sea urchin genome in hand, Eric Davidson become the leading liberator of quantitative principles of cell regulation, trapped in the qualitative, descriptive world of biology without genomic sequence.

In this talk we will discuss several computer science problems, inspired by our 15-year-long collaboration with Professor Davidson, who died in 2015, and rooted in his seminal research on causality, completeness, genomic Boolean logic, and genomically encoded regulatory information. Our collaboration produced the CYRENE cisGRN-Lexicon database containing the regulatory architecture of 600+ transcription-factor-encoding genes and other regulatory genes in eight species: human, mouse, fruit fly, sea urchin, nematode, rat, chicken, and zebrafish; and the CYRENE cisGRN-Browser, a full genome browser dedicated to cis-regulatory genomics.

Professor Davidson’s legacy consisted of 400+ papers and six books; he mentored about 300 Ph.D.s, postdocs and faculty in his laboratory in the Division of Biology at the California Institute of Technology. He was also a beacon of critical discourse. In this spirit, my presentation will include some critical comments about "computational systems biology considered harmful" avenues. As our beloved teacher and mentor, and like in his Caltech Laboratory, Davidson united us — biologists, physicists, biochemists, engineers, mathematicians and computer scientists, — in a research renaissance movement towards the quest for the functional meaning of DNA. From such research will ultimately come, by experimental demonstration, the revelation of the much sought-after laws of regulatory biology.

A time to model and a time to experiment

Michel Morange (Ecole Normale Supérieure, France)

The nature and role of models has been amply discussed by philosophers of science. They have emphasized the diversity of models and their functions. Biological sciences in general, and molecular and cellular biology (MCB) in particular, are no exceptions. The nature and role of models in MCB are also a legacy of the different disciplines that contributed to its formation. Models can be a step towards abstraction, or the opposite, a step towards a material representation of an - to date - abstract phenomenon. Models can also help to collect information and knowledge.

I will consider different models that played a highly important role in MCB, up to the Gene Regulatory Network model. There is a right time to model, and a right way to do it. I will try to understand why a model is well received (or not), and what kind of relationship it may or must have with experiments and experimental data.

Gene regulatory networks governing the generation and regeneration of blood and the cardiovascular system

Roger Patient (University of Oxford, U.K.)

Blood naturally regenerates throughout life, relying critically on a small number of stem cells found in the bone marrow. These cells provide life-saving transplants for blood diseases and cancers but their supply is limited. Expansion and/or generation of these hematopoietic stem cells (HSCs) in vitro would be transformative in the clinic. Current protocols to achieve this, including by differentiation of induced pluripotent stem cells or by reprogramming of somatic cells, only succeed at very low efficiencies. This is because our understanding of their genetic programming is incomplete. Using experimentally manipulable amphibian and fish model systems, we have tracked the cell lineage of blood stem cells during embryonic development and identified many of the extracellular signals that impinge on the cells as they move through the embryo. We have then begun to work out the gene regulatory networks established in the nuclei in response to those signals. This knowledge should lead to better protocols for blood stem cell production in vitro for the clinic.

Regeneration of cardiac muscle, after ischaemic injury for example, happens in humans at too low a frequency to replace sufficient numbers of cardiomyocytes to effect repair. However, the zebrafish heart regenerates well enough to re-establish normal function. This repair involves reactivating many of the gene regulatory networks responsible for heart development during embryogenesis. We have identified genetic circuitry common to both heart and blood/endothelial development which may suggest the presence of multipotent progenitors that generate the coronary vessels as well as the myocardium. Such cells, if retained or induced in the adult, would be strong candidates for the cells that drive regeneration after injury. We have profiled the expression in such a candidate population of cells and identified a signalling pathway that could contribute to the regeneration of coronary vessels as well as cardiomyocytes after injury. Clearly it would be interesting to determine the status of this pathway in the injured human heart.

The architecture of genomic programs for development

Isabelle S. Peter (California Institute of Technology, U.S.A.)

The animal body plan is defined by spatially organized discrete functional units such as organs, appendages and various distinct cell fates. During development, this spatial organization is

established by the operation of genomic control programs that parse the embryo into discrete domains of gene expression. Developmental gene regulatory networks (GRNs) consist of interacting regulatory genes and determine developmental expression of all genes. Although GRNs are encoded in individual cis-regulatory modules, higher levels of network organization also contribute to the developmental function of GRNs. Thus, a comparison of network architectures among GRNs operating in various developmental contexts indicates that developmental GRNs are composed of structurally, and possibly also functionally, related network architectures, or subcircuits. Several examples of these shared network architectures have been found in the GRN underlying specification of endomesodermal cell fates in sea urchin embryos, a network that has been exceptionally well characterized by experimental perturbation and cis-regulatory analyses. The overall developmental function of the endomesoderm GRN relies on controlling expression of endodermal and mesodermal regulatory states, a function that has been reproduced in silico by a Boolean computational model of this network. Computational modeling of the identified network subcircuits confirms that network architecture constrains developmental function. However, this Boolean logic analysis also indicates that developmental functions are not completely defined by the structure of network interactions; they also crucially depend on the regulatory logic encoded in individual cis-regulatory modules. Thus, in order to evaluate GRN function, both network architecture and the logic gates operating at each network node have to be considered as important determinants of developmental outcome.

Creating and buffering morphogen gradients: Combining computation and experimental approaches

Benny Shilo and Naama Barkai (Weizmann Institute of Science, Israel)

Morphogen gradients determine tissue pattern by triggering differential cell responses to distinct morphogen concentrations. The strict quantitative dependence of the emerging patterns on morphogen distribution raises the challenge of buffering variability in morphogen profile to ensure a reproducible outcome. We describe the underlying principles of two modules for buffering morphogen distribution: buffering morphogen amplitude by storing excess morphogen in a limited spatial region, and buffering morphogen spread by pinning morphogen levels at a distal position through global feedback that adjusts morphogen diffusion or degradation across the tissue. We also present concrete examples of patterning systems that implement these modules.

Dynamic control of the synthesis of DNA precursors (dNTP) in early embryos
Stanislav Shvartsman (Princeton University, U.S.A.)

Exponential increase of cell numbers in early embryos requires large amounts of DNA precursors (deoxyribonucleoside triphosphates (dNTPs)). Little is understood about how embryos satisfy this demand. We examined dNTP metabolism in the early Drosophila embryo, in which gastrulation is preceded by 13 sequential nuclear cleavages within only 2 hours of fertilization. Surprisingly, despite the breakneck speed at which Drosophila embryos synthesize DNA, maternally deposited dNTPs can generate less than half of the genomes needed to reach gastrulation. The rest of the dNTPs are synthesized “on the go.” The rate-limiting enzyme of dNTP synthesis, ribonucleotide reductase, is inhibited by endogenous levels of deoxyATP (dATP) present at fertilization and is activated as dATP is depleted via DNA polymerization. This feedback inhibition renders the concentration of dNTPs at gastrulation robust with respect to large variations in maternal supplies and is essential for normal progression of embryogenesis.

Modeling the chemical way: From cell structure to beta blocker. A brief history
Anthony S. Travis (Hebrew University of Jerusalem, Israel)

In the 1880s, medical researcher Paul Ehrlich (1854-1915) developed a repertoire of differential stains based on the new synthetic dyes and used their colour changes as they underwent reduction to locate sites of biological combustion within animals. By comparing the behaviours of different dyes, he made semi-quantitative measurements of oxygen uptake and suggested a model for features of cell surfaces. In 1897, using this model, he developed his side-chain theory to account for formation of antibodies and the specificity of their relationship with homologous antigens. He then went on to attack sites of disease within the body. In 1909, jointly with Sahaschiro Hata, he discovered the curative action of a dye analog, compound 606 or arsphenamine, which was marketed by the Hoechst dyeworks as Salvarsan. Around 1960, James Black at ICI Pharmaceuticals in the UK used a derivative of Ehrlich’s model to explore the idea of blocking specific biochemical pathways in the body to cure diseases. He developed the first of the beta-blockers for high blood pressure and heart diseases. Later, at Smith, Kline & French, he developed cimetidine, the first H2-blocker for stomach acidity.