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Chapter 1 : Hypothesis-Free? No Such Thing | The Scientist MagazineÂ®

Schwabe's hypothesis that all species on earth have an independent but natural origin, is a remarkable, non-creationist, unorthodox theory of the origin of calendrierdelascience.com describe his theory as a 'multiple origins' theory is an understatement, because we are talking about a billion living and extinct species.

Overview[edit] While some scientists, such as Freese [2] and Freese and Yoshida , [3] had suggested that neutral mutations were probably widespread, a coherent theory of neutral evolution was proposed by Motoo Kimura in , [4] and by King and Jukes independently in As a result, the theory regards these genomic features as neither subject to, nor explicable by, natural selection. This view is based in part on the degenerate genetic code , in which sequences of three nucleotides codons may differ and yet encode the same amino acid GCC and GCA both encode alanine , for example. Consequently, many potential single-nucleotide changes are in effect "silent" or "unexpressed" see synonymous or silent substitution. Such changes are presumed to have little or no biological effect. A second hypothesis of the neutral theory is that most evolutionary change is the result of genetic drift acting on neutral alleles , rather than for example genetic hitchhiking of a neutral allele due to genetic linkage with non-neutral alleles. After appearing by mutation, a neutral allele may become more common within the population via genetic drift. Usually, it will be lost, or in rare cases it may become fixed , meaning that the new allele becomes standard in the population. This stochastic process is assumed to obey equations describing random genetic drift by means of accidents of sampling. This means that if all mutations were neutral, the rate at which fixed differences accumulate between divergent populations is predicted to be equal to the per-individual mutation rate, e. When the proportion of mutations that are neutral is constant, so is the divergence rate between populations. This provides a rationale for the molecular clock , although the discovery of a molecular clock predated neutral theory. Positive selection can, in turn, be further subdivided into directional selection , which tends toward fixation of an advantageous allele, and balancing selection , which maintains a polymorphism. The neutral theory of molecular evolution predicts that purifying selection is ubiquitous, but that both forms of positive selection are rare, whereas not denying the importance of positive selection in the origin of adaptations. Positive selection is a relative rarityâ€”but of great interest, precisely because it represents a departure from the norm. Contrary to the perception of many onlookers, the debate was not about whether natural selection does occur. Kimura argued that molecular evolution is dominated by selectively neutral evolution but at the phenotypic level, changes in characters were probably dominated by natural selection rather than genetic drift. Levels of genetic diversity vary much less than census population sizes, giving rise to the "paradox of variation". Tomoko Ohta emphasized the importance of nearly neutral mutations, in particularly slightly deleterious mutations. There are a large number of statistical methods for testing whether neutral theory is a good description of evolution e. However, Nei et al.

Chapter 2 : An epigenetic hypothesis for the genomic memory of pain

The Genomic Potential Hypothesis is a biochemist's view of the origin, evolution, and development of life. Large numbers are second nature to a biochemist and though he rarely ever thinks of it explicitly, the concept of mass action is a part of the definition of chemistry.

Received Oct 15; Accepted Feb The use, distribution and reproduction in other forums is permitted, provided the original author s or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms. This article has been cited by other articles in PMC. Abstract Chronic pain is accompanied with long-term sensory, affective and cognitive disturbances. What are the mechanisms that mediate the long-term consequences of painful experiences and embed them in the genome? DNA methylation is an epigenetic mechanism for long-term regulation of gene expression. Neuronal plasticity at the neuroanatomical, functional, morphological, physiological and molecular levels has been demonstrated throughout the neuroaxis in response to persistent pain, including in the adult prefrontal cortex PFC. We have previously reported widespread changes in gene expression and DNA methylation in the PFC many months following peripheral nerve injury. In support of this hypothesis, we show here that up-regulation of a gene involved with synaptic function, Synaptotagmin II syt2 , in the PFC in a chronic pain model is associated with long-term changes in DNA methylation. The challenges of understanding the contributions of epigenetic mechanisms such as DNA methylation within the PFC to pain chronicity and their therapeutic implications are discussed. Rather than the pain itself, these higher-order functions, mediated by supra-spinal structures, can have the biggest impact on quality of life in chronic pain patients Nicholson and Verma, Chronic pain changes brain anatomy and function. Studies in rodent models of chronic pain have demonstrated pain-related modifications in areas including the hippocampus, amygdala, perirhinal cortex, and prefrontal cortex PFC; Seminowicz et al. These findings extend to humansâ€”multiple studies have reported decreased gray matter, reduced cortical thickness, abnormal cortical function, and altered connectivity in various brain regions in a wide range of chronic pain conditions including low back pain Giesecke et al. The magnitude of these changes has been related to the duration and the intensity of chronic pain Apkarian et al. While changes in some brain regions are associated with specific chronic pain conditions, most studies report changes in common areas involved in pain modulation, including the PFC Apkarian et al. Interestingly, the PFC has been implicated in depression, anxiety and cognitive impairment, all of which are frequently associated with chronic pain. Pain-related pathological changes in the PFC may therefore contribute to the emergence of emotional and cognitive impairments. In order to determine if chronic pain could induce pain-related changes in brain anatomy, Seminowicz et al. Consistent with the human literature, pain-related decreases in frontal cortex volume were observed in rats subjected to peripheral nerve injury as adults. These changes were not observed until approximately 4 months post-injury and were temporally correlated with the development of anxiety-like symptoms in the same animals. Thus, pain-related changes in the PFC are a consequence of chronic, but not acute pain. For example, basal dendrites had longer branches in the PFC in animals with peripheral nerve injury than in controls Metz et al. Changes in neuroanatomy are also linked to functional differences within the firing of pyramidal neurons Centeno et al. Ongoing chronic pain not only induces changes in the PFC but also actively maintains them. We have shown that pathological changes in the PFC in individuals with chronic low back pain cLBP can be reversed with effective pain management Seminowicz et al. Specifically, cLBP-associated cortical thinning in the dorsolateral PFC DLPFC was reversed post-treatment, and the magnitude of this reversal correlated with the reduction of both pain and physical disability. Furthermore, abnormal activity in the DLPFC during an attention-demanding cognitive task in cLBP patients was reduced towards normal levels following treatment. For example, increased physical activity resulted in improved memory and increased local gray matter volume in the PFC in adult volunteers Ruscheweyh et al. These data indicate that long-term structural and functional brain abnormalitiesâ€”specifically in the PFCâ€”are induced by chronic pain. Furthermore, they suggest that treating chronic pain can restore normal brain function in the

adult human PFC and raise the possibility that therapies targeting pathological changes in the PFC have therapeutic utility. Finally, the reversibility suggests that these changes are unlikely to be due to neurotoxicity; in contrast, the underlying mechanisms must be both long-lasting and reversible. Pain-Related Changes in Gene Expression in the Adult Prefrontal Cortex Given the extensive structural and functional abnormalities in the PFC associated with pain persistent changes in genomic programming are likely to contribute to both chronic pain and to the associated co-morbidities. For example, in a model of acute facial pain, genes related to immune function and neutrophil activation are over-expressed in the PFC Poh et al. In chronic neuropathic pain, we observed differential RNA expression of genes. Some of these genes are associated with functional pathways involved in neuronal development, cell differentiation and growth in the PFC 6 months following peripheral nerve injury Alvarado et al. That is, narrow and weak promoters represent tissue specific and general cell cycle processes, respectively. This suggests that transcriptional landscape is accompanied with changes that are enriched for tissue-specific changes than those involved with the general cell cycle. Given the scope of long-term anatomical changes and the large number of differentially expressed transcripts, the transcriptional machinery itself is likely to become dysregulated as chronic pain progresses. Within upregulated transcriptional networks, we identified pathways that were relevant to cellular growth, differentiation, structural function and neuronal function Alvarado et al.

Chapter 3 : The genomic potential hypothesis and phase-state mathematics - CORE

The genomic potential hypothesis predicts that humans came about by the mechanism that also produced arthropods (Schwabe,). All of them were read from the surface of the genome of their specific stem cells like the first arthropods, but in this case with a few more sentences, paragraphs, and subtitles.

Even so-called "discovery-driven research" needs a hypothesis to make any sense. May 1, Steven Wiley Following a recent computational biology meeting, a group of us got together for dinner, during which the subject of our individual research projects came up. After I described my efforts to model signaling pathways, the young scientist next to me shrugged and said that models were of no use to him because he did "discovery-driven research". He then went on to state that discovery-driven research is hypothesis-free, and thus independent of the preexisting bias of traditional biology. I listened patiently, because I have heard this argument many times before. I was too polite to point out that all biological research was hypothesis-driven, although the hypothesis might be implicit. Genomic sequencing projects might seem to lack a hypothesis, but the resulting data is exploited by hypothesizing specific evolutionary relationships between different genes. The idea there are actually two distinct ways of conducting biological research was formally proposed several years ago in a Nature Biotechnology commentary R. The authors described "discovery science," like genome sequencing projects, as blindly cataloguing the elements of a system, disregarding any hypotheses on how it works. In contrast, they described "hypothesis-driven science" as being small-scale, narrowly focused, and using a limited range of technologies. To imply that large-scale systems biology research can be productively conducted without a prior set of underlying hypotheses is nonsense. A good hypothesis is at the heart of the best science, regardless of scale. We started our systems biology program almost eight years ago, and one of our first projects was to establish the relationship between specific cell signaling pathways and both gene and protein expression. We thought that important patterns would quickly become self-evident, but sorting through lists of thousands of genes and proteins quickly dissuaded us of that idea. We could see patterns, but they simply did not make any obvious sense. We mostly know the relationship between gene expression and subsequent protein levels, but looking at thousands of genes made it seem more complex, and overwhelmed our intuition. To extract biological meaning from the data required a level of simplification. And this is where we needed a hypothesis. By postulating that specific classes of proteins were degraded at an accelerated rate, for example, we could create hypothetical patterns against which to compare our data. This allowed us to quickly look for both expected and unexpected relationships. After our initial, disappointing foray into "discovery science", we subsequently used specific hypotheses to guide our experimental designs. For example, by proposing that signaling pathways regulate the shedding of proteins from the cell surface, we were able to identify these proteins, relate them to specific signaling pathways, and discover that they are frequently released by cancer cells Jacobs et al. Despite the importance of hypotheses in systems biology research, they are not always explicitly stated. As biologists, we are well trained in posing small, specific questions, but we have little familiarity with framing systems-level hypotheses. Unlike small questions, systems-level hypotheses might take the form of postulating how the outputs from different signaling pathways are combined. Likewise, our intuition regarding systems-level relationships in biological systems is difficult to translate into experimental design. This is why computational models are so central to systems biology research. Unlike humans, computers are very good at keeping track of complex relationships and predicting how low-level changes will alter higher-level functions. Computational models, however, must be built from a set of explicit, hypothesized relationships. Finding meaningful relationships in complex datasets also requires starting with the appropriate data. A hypothesis usually takes the form of a mechanistic relationship between a specific cause and a consequent effect, and this will almost always depend on experimental context. There are some circumstances when data must be gathered in the absence of context or hypothesis to characterize a system, but it is unrealistic to expect such preliminary studies to lead to significant biological insights. For this, you need a hypothesis. Systems biology might be the future of biology, but we still need hypotheses to take us where we want to go.

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Chapter 4 : Neutral theory of molecular evolution - Wikipedia

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Chapter 5 : Multiregional origin of modern humans - Wikipedia

In contrast, the genomic potential hypothesis is a "post-data" model that was innocently built upon the new information and the results do not point to a random chance-oriented model but rather to a deterministic, yet unpredictable one.

Chapter 6 : Contact Support

While this concept applies to molecular interactions in general, there is nowhere a more impressive demonstration of a principle that is central to life and central to the Genomic Potential Hypothesis than this threshold of information production.

Chapter 7 : Project MUSE - A Polyphyletic View of Evolution: The Genetic Potential Hypothesis

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