



100 YEARS AGO

In a paper on the energy of the universe in the *Revue scientifique*, M. I. Skvortzow discusses the influence of electrical phenomena in cosmogony. He considers that in the past history of the earth, and of other celestial bodies, electrical and chemical energy have originally played the most important part, and that heat energy has become more and more important in proportion as the earth has assumed a more material form... The heat of the earth M. Skvortzow attributes to electric currents circulating mostly near the surface; the interior of the earth, on the other hand, he thinks may be as cold as the greatest depths of the ocean. Changes in the aspect of the earth, as well as meteorological phenomena, are attributed to electric currents induced by solar influence. The temperatures of different planets are considered to depend less on their distance from the Sun than on their reserve of energy and on the currents which the Sun induces in them in virtue of their axial and orbital motions. Will this theory of the electromagnetic origin of the earth's heat reconcile the two opposing views on the age of the earth?
From *Nature* 30 January 1902.

50 YEARS AGO

A new periodical is apt to arouse suspicion and evoke the question, "Is it really necessary?" It may be said that two conditions must be fulfilled for a newcomer to be regarded as a journal of importance: the first is that the contents must be of high quality; and the second that it serves as a medium for publishing work which might not otherwise reach those to whom it is of interest. As regards the first requirement, there can be little doubt of its fulfilment by *Chemical Engineering Science: Genie Chimique*, an international monthly the first number of which appeared last October... There are seven editors, all chemical engineers of high standing, residing in France, Great Britain, Italy, Switzerland, Belgium, Holland and Norway, and an advisory board of nineteen from eleven countries. Six original papers of high quality occupy fifty quarto pages very clearly printed by the Würzburg University Press, and it is hoped to publish in English, French or German not only papers dealing with the principles of chemical engineering but also detailed notes on advances in industrial processes.
From *Nature* 2 February 1952.

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Bacterial behaviour

Function by serendipity

Dagmar Ringe

Crystallography has provided an unusual route to the characterization of a bacterial signalling agent: the molecule concerned has been accidentally caught in the clutches of its receptor.

In most of biology, research projects usually follow a hypothesis-driven path that starts with the identification of some activity or other and leads to knowledge of the detailed functions of the molecules responsible. Ultimately, complete characterization of function requires information at many levels of organization, and experiments of many kinds.

For instance, in the case of the signalling pathway described by Chen *et al.* on page 545 of this issue, the activity that was originally identified is the ability of bacteria to communicate with each other. A complete description of the phenomenon would include the chemical composition of the signalling molecule or molecules, the atomic structures of the target receptor(s) on the bacterial cell wall, how the molecule interacts with the receptor, and a description of the ensuing pathways inside the cell that produce the response.

In their paper, the authors describe two parts of this characterization: the chemical composition of the signalling molecule and the atomic structure of the target receptor (Chen, X. *et al. Nature* **415**, 545–549; 2002). The serendipitous result of their efforts to obtain one led to the characterization of the other. Determining the three-dimensional structure of the sensor protein, LuxP, accidentally provided the structure of the signalling molecule, AI-2, because it co-purified with the sensor. This enabled Chen *et al.* to identify AI-2 as a boron-containing molecule — a furanosyl borate diester. This remarkable observation suggests a role for boron in the cell, as well as providing the identity of a signalling protein used in bacterial communication.

Bacteria can communicate with each other by extracellular signalling molecules called autoinducers. These molecules are often specific to a particular species of bacterium, and coordinate processes such as production of 'virulence factors' (which are involved in defence or attack). In the mid-1990s, AI-2, a general, nonspecific signalling molecule, was discovered. But AI-2's chemical identity proved elusive until its trace appeared in the electron-density map of its LuxP receptor, seen by Chen and colleagues using protein crystallography. This technique, then, can still be considered an analyti-

cal tool for identifying molecules that cannot be characterized by other methods. Moreover, Chen *et al.* find that an unusual element is involved — boron, to which a specific cellular role had not previously been assigned.

Boron is a trace mineral that is potentially toxic to all organisms. In the form of boric acid and borax, it is used as a pesticide and food preservative, and antiseptics containing boric acid are still a common source of accidents in young children. Boron is an essential mineral for green algae and higher plants, but no such role has yet been demonstrated for any other organism. The element might be involved in human brain function, alertness and cognitive performance, and in mineral metabolism. It might also reduce the symptoms or incidence of arthritis. But these are just possibilities: they don't help to establish that boron is an essential element in these circumstances, let alone define its cellular function. Chen and colleagues' discovery that boron is part of a signalling molecule in bacteria defines such a function.

The serendipitous characterization of the AI-2 autoinducer molecule is most intriguing. We live in an age of discovery fuelled by an explosion of gene-sequence information. The genetic make-up of organisms at all levels of the evolutionary ladder is being determined so rapidly that it is becoming increasingly difficult to keep up with the interpretations of the functions for gene products.

At present, these interpretations depend heavily on comparisons between genes that encode proteins of unknown function and those coding for proteins whose functions have been studied by classical biochemical and genetic methods. But it is unlikely that we will ever be 100% successful in identifying function by comparing amino-acid sequences. In part, this is because proteins from different organisms may be related by sequence but have very different functions. Sequence codes for the architecture of the protein, as well as the identity of an active or interaction site, so these two properties may not be preserved simultaneously. In addition, the identity of another molecule that interacts with a given protein cannot be deduced from its sequence.

The three-dimensional structure can be a

powerful ally when trying to identify the function of a protein whose sequence is unrelated to that of any other. At this level, however, surprises still occur. A sequence that is not related to that of a protein of known structure can nevertheless fold into an architecture that is already well characterized. In other words, the same three-dimensional protein fold can be derived from completely unrelated sequences. Moreover, although two proteins may be unrelated in sequence and structure, their active sites may be alike and identical in the job they carry out: a protein's function can be derived from more than one architecture.

Structure determination can also deliver a surprise when another molecule unexpectedly comes along for the ride. In these instances, the first assumption is that the bound molecule is specific for the protein and is therefore involved in what it does. That seems to be the case with the signalling

receptor LuxP, where the bound molecule is presumed to be the signalling molecule, AI-2. Chen *et al.* were able to establish the identity of AI-2 at the same time as seeing its interaction with the receptor.

The overall message then, is this. To provide a complete functional description of a gene product, information from many types of experiment has to be integrated. Hypothesis-driven research leads to clearly designed experiments that test well-defined ideas. Discovery-driven research is designed to find new correlations from a sea of information that is being generated for its own sake. The combination of the two should prove to be more powerful than either alone in identifying the cellular roles of undefined gene products. ■

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Biogeography

Big thinking

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Since the demise of the dinosaurs, no land vertebrate has matched them for size. Why? The answer may lie in the particular conditions prevailing in the Cretaceous period.

How does evolution produce giant land vertebrates? One of the prerequisites for making such creatures appears to be the existence of big continents¹⁻³. Writing in *Proceedings of the National Academy of Sciences*, however, Burness *et al.*⁴ demonstrate that the largest animals also eat plants and are cold-blooded.

The authors have analysed data on the largest vertebrate herbivores and carnivores from 30 islands and continents. For each land mass, the authors identified either the largest living species of vertebrate land animal or the largest species that became extinct within the past 65,000 years. They show that, for a land mass of a given size, the largest warm-blooded herbivore was bigger than the largest warm-blooded carnivore. Data for cold-blooded land vertebrates are sparse, because so few of them are the largest vertebrate on a land mass. But, for a given land mass, the authors show that cold-blooded carnivores were larger than warm-blooded carnivores. Similarly, the three data points on cold-blooded herbivores suggest that they are larger than warm-blooded herbivores. Burness and colleagues then go on to evaluate the factors that may have been responsible for the evolution of large dinosaurs.

Like many ecological relationships, that between maximum body mass and land area is a power function⁴. That is, if M is the maximum body size of a group of terrestrial

vertebrates on a particular continent, and A is the area of that continent, then $M = kA^b$. Burness *et al.* found that the exponent b effectively equals 0.5, but that the constant k differs among warm- and cold-blooded herbivores and carnivores. The largest warm-blooded herbivore on any given land mass is roughly an order of magnitude larger than the biggest warm-blooded carnivore, if there is one. The few data that are available suggest a similar relationship for cold-blooded vertebrates.

Why should the largest carnivores be smaller than the largest herbivores? It is well established in ecology that the energy available to organisms declines by about 90% for each step up the food chain. So it is reasonable to expect that the largest size a carnivore can reach will be about 10% of the size of the largest herbivore on the same land mass.

Given a specific power function that describes the relationship between maximum body size and continental area for a given group of organisms, how does such a relationship arise? If maximum body mass is controlled in some manner by continent size, then continent size must be related to the minimum number of individuals in the geographical population of a large-bodied species. Each individual of a species of a given size requires a certain minimum amount of space within which to obtain resources and mates. This space, the organism's 'home range', is larger for animals of larger body

size⁵. The relationship between home range size, H , and body size is also a power function: $H = aM^z$. The total number of home ranges available for a species of a given size on a given continent will be the continent size divided by the size of that species' home range. After a little algebra, one can deduce that b (the exponent for the power function relating maximum body mass to continent size) should be the inverse of z (the exponent for the power function relating home range to body mass).

Testing whether $b = 1/z$ is true for the largest animals on islands and continents isn't entirely straightforward. Data to test this idea are currently available only for mammals, not reptiles or amphibians. There are no instances where the largest mammal on an isolated island or continent is less than about 100 g in mass². So although many mammals are smaller than 100 g, the test will be valid only for those greater than 100 g. Given these restrictions, Burness *et al.* analysed some previously published data². When they fitted a power function to the sizes of large mammals as a function of their territory size, the resulting exponent was very close to 0.5, confirming the prediction. So large mammals are found only on large continents because small continents don't have enough space to maintain adequate populations of them.

Where do dinosaurs fit into the relationship between maximum body size and continent size? If dinosaurs were warm-blooded

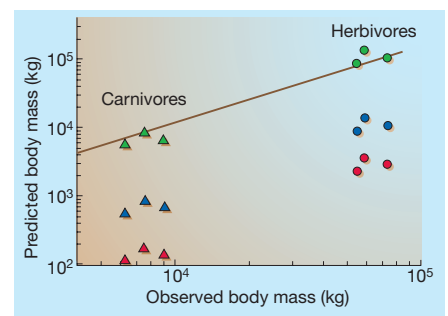


Figure 1 Why were the biggest dinosaurs so huge? Shown in red and blue are estimates of the sizes of several of the largest herbivorous (circles) and carnivorous (triangles) dinosaurs derived from modern relationships between continent size and maximum body size⁴. It is still not known whether dinosaurs were warm- or cold-blooded. Estimates made using relationships for warm-blooded modern vertebrates (red) are two orders of magnitude lower than the actual sizes (solid line); but those using relationships for cold-blooded vertebrates (blue) are still an order of magnitude lower. A possible explanation for the failure of these estimates, proposed by Burness *et al.*⁴, is that the productivity of terrestrial vegetation was ten times higher in the Cretaceous period, between 144 million and 65 million years ago, when dinosaurs reached their largest sizes. That vast extra productivity allowed animals to evolve that were an order of magnitude larger than those that modern continents can support (green symbols).