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SYNTHETIC BIOLOGY

It's an analog world

The first synthetic genetic circuits to use analog computation have been developed. These circuits involve fewer components and resources, and can execute more complex operations, than their digital counterparts. SEE LETTER P.619

HERBERT M. SAURO & KYUNG HYUK KIM

The engineering of biological networks, a discipline called synthetic biology, has seen remarkable progress since its inception in 2000. The fact that we can now design simple but functional circuits *in vivo* is probably one of the most important aspects of this progress — it suggests that our biophysical understanding of the cellular milieu is largely correct, even if many details remain to be resolved. The significance of this should not be underestimated, because it means that predictive engineering of new cellular networks and systems is possible. Until now, approaches to synthetic biology have been greatly influenced by the digital computing technology that we use every day. But biological cells do not process information in a solely digital fashion; rather, they carry out many operations in an analog manner. In this issue, Daniel *et al.*[1] (page 619) break the mould and venture into a completely new area of synthetic biology, presenting synthetic circuitry that can perform analog calculations*.

Synthetic biology has already led to several notable firsts — from the construction of switches, oscillators and feed-forward networks to the creation of gene regulatory circuits that can carry out Boolean logic. In many ways, digital computing has coloured our approach to synthetic biology. It is a truly remarkable achievement that so much can be done with just the 'ones' and 'zeros' that form the basis of digital processing. After more than 60 years of digital computing, it is no surprise that many modes of thinking have become highly influenced by the digital paradigm. It is often said that a biological cell is just like a digital computer, and that reprogramming a cell is like writing software. But the digital analogy is a misleading one, because many processes that occur in a biological cell have no counterpart in a digital computer. If reprogramming a cell was just a case of writing code, then re-engineering cells would be simple — but it is not.

*This article and the paper under discussion[1] were published online on 15 May 2013.

The reality is that cells use a hybrid approach to information processing. In some cases they use digital yes-or-no decisions, but in many cases cellular signals are analog, with levels of gradation. More exotic, little understood signal-processing techniques involving noise and other forms of signal probably also contribute. And on top of that, a complex chemistry exists that continuously reassembles the cell in real time.

Nevertheless, constructing digital devices is both a useful and an interesting engineering challenge for synthetic biologists, and many advances have been made in mimicking digital systems either *in vivo* or *in vitro* using DNA as components. One remarkable study was the construction of an *in vitro* 4-bit square-root calculator consisting of 130 DNA strands[2]. Another was the construction of an *in vivo* system to detect four different inputs, comprised of four sensors and three logic gates[3].

"The ability to process graded information by means of synthetic biological circuits will be of interest to many researchers."

Although these are significant achievements, such circuits require large numbers of components to perform even the simplest computation. A 4-bit binary adder, for example, might require 30 or more proteins to operate, and at the same time would place a substantial metabolic burden on a cell. More challenging and perhaps more interesting is to attempt to mimic analog computation in a cell, as Daniel *et al.* have done.

One key advantage of analog over digital is that far fewer devices are needed to carry out a given computation at the moderate precision needed in cells[4], and fewer devices mean lower resource requirements. In addition, the richness of signal processing that can be carried out in analog systems is far greater than what can be accomplished in digital systems using the same number of components. But analog information processing brings with it a new set of challenges. Compared with that of digital systems, the design of analog circuitry requires greater expertise in feedback-system design, circuit theory and signal processing. Daniel and colleagues' work is founded on the close analogy they saw between the exponential thermodynamic electron flow that occurs in transistors and the exponential thermodynamic rates seen in chemical reactions[5]. This similarity led them to realize that analog electronic circuits that operate in the logarithmic domain might be effective mimics of analog biological circuits that operate in the logarithmic domain.

To test this idea, Daniel *et al.* constructed a gene-transcription unit in which the concentration of a transcription factor (a protein that regulates gene transcription) could be logarithmically transformed over a wide range of concentrations, thus enabling fine control of gene expression.

Moving an input signal into the logarithmic domain has many benefits, especially that basic calculations such as division and multiplication can be more easily executed in log space. The core of the authors' logarithmic unit is a positive-feedback loop operating in an analog mode. A shunt is included that removes excess transcription factor so as to increase the range of operation and efficiently implement positive feedback. With this basic logarithmic unit in place, the researchers could then focus on adding higher-order functions. For example, by attaching a repressor module, they created a circuit whose readout was the negative of the log of the input. Another circuit simply summed the activity of two parallel logarithmic circuits to mimic a multiplication operation.

Furthermore, using just two transcription factors, the authors were able to create a negative-feedback analog circuit that scaled the logarithmic function. Especially interesting was their construction of a circuit that computed the ratio of two inputs over four orders of magnitude of input concentration. Computing a ratio might have many applications, such as normalizing or comparing values, or even providing an *in vivo* pH meter.

The ability to process graded information by means of synthetic biological circuits will be of interest to many researchers. For example, most inputs from the environment are graded, and a synthetic circuit with a fluorescent protein readout might be able to represent the rate of change of an environmental input rather than its absolute level. This could be accomplished by having an analog differentiator circuit. Other analog designs might be used to measure the weighted sum of environmental inputs, such that when a particular combination of inputs is reached it triggers a change in the state of the cell. Designing such analog circuitry may also further our understanding of natural systems. The function of many regulatory systems in cells remains obscure, and studies of synthetic biology in the analog domain should lead to

new theories on how biological systems process information, and thus allow such systems to be more finely controlled. ■

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PALAEOANTHROPOLOGY

Hesitation on hominin history

Extensive studies of fossil skeletons of *Australopithecus sediba* provide fascinating details of the anatomy of this hominin species, but do not convincingly indicate its position on the evolutionary route to modern humans.

WILLIAM H. KIMBEL

The evolutionary events that led to the origin of the *Homo* lineage are an enduring puzzle in palaeoanthropology, chiefly because the fossil record from between 3 million and 2 million years ago is frustratingly sparse, especially in eastern Africa. Much attention has been paid to two fossilized skeletons, found in approximately 2-million-year-old sediments at the Malapa cave site in South Africa, that are recognized as representing the species *Australopithecus sediba*. These have been the focus of scrutiny because of both their excellent preservation and claims[1,2] that this hominin — a species more closely related to humans than to chimpanzees — lies at the base of the *Homo* lineage. A series of reports published in *Science*[3–8] sheds light on the morphology of *A. sediba* but, in my view, does little to elucidate its role in later human evolution.

Dental morphology is a frequent source of information about hominin phylogeny but, in the first of these new papers, Irish *et al.*[3] take the unconventional step of using only the Arizona State University Dental Anthropology System — a graded series of minor crown variants originally devised to distinguish recent human populations from one another — to decipher relationships between hominin species that are millions of years old. I have serious doubts about the phylogenetic meaning of morphological similarity in this case. These concerns are compounded by the authors' reliance on the gorilla as the sole outgroup in their cladistic analysis. Their results link *A. sediba* exclusively to *Australopithecus africanus*, an older (approximately 2.7 million to 2.3 million years old), potentially ancestral, southern African species with which it also shares some key cranial features[1]. If this finding is borne out by further work, then the relevance of *A. sediba* to the origin of *Homo* would be inextricably tied to that of *A. africanus*, whose own position in hominin phylogeny is by no means settled[9].

De Ruiter and colleagues' analysis of the *A. sediba* mandible[4] includes a measurement-based comparison in which the sub-adult individual MH1(with only its second molar erupted) is treated as though its growth had been completed. However, for most dimensions, hominoid mandibles achieve only around 75–90% of their adult values by the time of the second molar eruption[10]. So, although the *A. sediba* mandibles seem to be small and lightly built (and thus *Homo*-like) by australopith standards, it is unclear how much of this impression is due to the authors' use of a sample comprising a sub-adult and a presumed adult female (MH2).

Much of the value of the Malapa material lies in the extremely rare association of upper and lower limb parts with elements of the axial skeleton in two individuals of the same species (Fig. 1). These skeletons paint a portrait of a pectoral girdle that retains more ape-like anatomy than the pelvic girdle[5,11]. Churchill *et al.*[5] report that a fairly complete scapula (from MH2) features an upwardly tilted articulation for the humerus and a relatively broad attachment area for a muscle that helps to lift the arm over the head, a familiar australopith upper-limb pattern that also includes long, strong forearms and curved fingers. Although these features are embedded in a terrestrial bipedal frame, they are often interpreted as signs of retained ancestral arboreal climbing behaviour[5,12]. Still unsettled is what led to the refashioning of the hominin shoulder by the time, around 1.6 million years ago, of *Homo erectus*, a species that shows modern upper-limb and shoulder morphology (this anatomy is unknown in the approximately contemporaneous *Homo habilis*). Simply leaving the trees seems to be an insufficient explanation.

Schmid *et al.*[6] used the low curvature of the upper ribs of *A. sediba* to argue for a conical ribcage and elevated shoulders similar to those of the great apes, even though second- and fourth-rib curvatures do not actually distinguish apes from humans. However, it is clear that the unusually strongly curved first rib articulates only with the first thoracic vertebra, as in humans and *Australopithecus afarensis*. This configuration is at odds with a completely ape-like upper thorax and has been associated with descent of the shoulder after the upper limbs were freed from locomotion[13], although this interpretation has been contested[14]. A further puzzle is the *A. afarensis* partial skeleton KSD-VP 1/1, which, although 1.6 million years older than the *A. sediba* skeletons, has

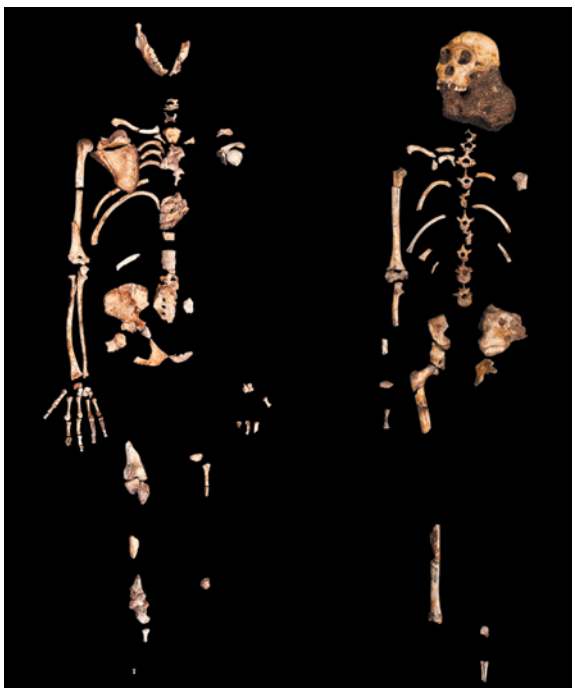

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Figure 1 | *Australopithecus sediba*. A series of papers[3–8] presents extensive studies of these two fossil skeletons, which date to approximately 2 million years ago. The authors compare the anatomy of this hominin to that of other species of the *Australopithecus* and *Homo* genera.