data of Bai *et al*. indicate that amino acids decrease the FKBP38-mTOR interaction and increase binding of FKBP38 to Rheb-GTP, consistent with FKBP38 involvement in amino acid control of mTORC1. However, decreasing the amount of FKBP38 in cells did not prevent the dephosphorylation of 4E-BP1 that occurs when cells are starved of amino acids. This suggests that the control of mTORC1 signaling by amino acids does not require FKBP38.

Although there are still important gaps in our understanding of mTOR signaling, the identification of FKBP38 as a regulator of mTOR clarifies previous observations about signaling events in this pathway. This is good news for developing alternative drugs that are not rapalogs to treat diseases that involve mTOR.

References

1. J. B. Easton, P. J. Houghton, *Oncogene* **25**, 6436 (2006).
2. C. H. Lee, K. Inoki, K. L. Guan, *Annu. Rev. Pharmacol. Toxicol.* **47**, 443 (2007).
3. X. Bai *et al.*, *Science* **318**, 977 (2007).
4. S. Wullschleger, R. Loewith, M. N. Hall, *Cell* **124**, 471 (2006).
5. J. Avruch *et al.*, *Oncogene* **25**, 6361 (2006).
6. X. Long, Y. Lin, S. Ortiz-Vega, K. Yonezawa, J. Avruch, *Curr. Biol.* **15**, 702 (2005).
7. X. Wang, C. G. Proud, *Physiology* **21**, 362 (2006).
8. B. D. Manning, L. C. Cantley, *Trends Biochem. Sci.* **28**, 573 (2003).
9. M. Rosner, K. Hofer, M. Kubista, M. Hengstschlager, *Oncogene* **22**, 4786 (2003).
10. D. H. Kim *et al.*, *Cell* **110**, 163 (2002).
11. E. Jacinto *et al.*, *Nat. Cell Biol.* **6**, 1122 (2004).
12. X. Wang, A. Beugnet, M. Murakami, S. Yamanaka, C. G. Proud, *Mol. Cell. Biol.* **25**, 2558 (2005).
13. X. Long, S. Ortiz-Vega, Y. Lin, J. Avruch, *J. Biol. Chem.* **280**, 23433 (2005).

10.1126/science.1150653

COMPUTER SCIENCE

Is There Progress on Talking Sensibly to Machines?

Several research projects are closing in on ways to allow humans to effectively communicate with machines in natural language.

Yorick Wilks

Since the earliest days of computing, people have sought ways to communicate with computers in "natural" language, rather than program them in symbolic languages like FORTRAN and C. In the 1960s, MIT researcher Joseph Weizenbaum's ELIZA program was an entertaining simulation of a Rogerian therapist (*1*). ELIZA took words you had used and played them back, as in: "Tell me why you feel like that about your family?" It is an irony of the brief history of machine dialog programs that ELIZA is remembered and PARRY is not. PARRY ran on the early ARPAnet at Stanford in the late 1960s and was designed by Kenneth Colby, a psychiatrist who wanted to model paranoiacs and their beliefs (*2*). PARRY was paranoid about the Mafia, horse races, track betting, and Italian-Americans; if anything you typed could be linked to them, it would spew out a paragraph of invective.

PARRY was more fun than the better-remembered ELIZA, and is another example of the "Betamax principle" (*3*). PARRY was based on nothing that could be called a theory; it was closer in spirit to the principal approach for studying machine dialog today, which could be captured as "big data + small theory." That is, PARRY had a tiny matching program and a very large set of hand-crafted data: about 6000 patterns it tried to match to whatever was typed to it.

In the PARRY/ELIZA years, artificial intelligence research typically took logic to be the core of machine intelligence, and linguistics was still strongly influenced by Noam Chomsky at MIT; both AI and linguistics assumed that small sets of axioms or grammar rules explained large sets of data, i.e., proved theorems or sentences. But neither approach actually had any real data at all, only a few made-up examples, whereas PARRY at least had the large set of patterns made up by its researchers. Any match found pointed to a set of possible replies. This kind of an approach was, and is, anathema to Chomsky, who said that data gathering is like pre-Galilean physics and can have no role in formal linguistics (*4*). The underlying problem with machine dialog, viewed as a technology, was that programs based on logic or on formal linguistic grammars had had little success for more than 40 years in producing usable computational artifacts.

All this changed in 1990, with the astonishing success of Frederick Jelinek's team at IBM (*5*). Originally speech-processing engineers working on the automatic transcription of speech into written form, they decided to apply their data-driven methods to machine translation, using as data 200 million words of parliamentary proceedings in parallel English-French text. The method was a statistical one that learned from the parallel text data what translation was but without creating any rules at all. This was the first important work in applying machine learning to language processing. Jelinek and his co-workers were not completely successful, but they had a success rate of about 50% in translating sentences that the program hadn't seen before.

Conversational companion. The Nabaztag rabbit (*11*) shows the feelings of a remote sender by speech, changing colors, and moving its ears. The speech is generated via a wireless Internet connection from typed input at a Web site. As an initial incarnation of a companion, the Companions project (*9*) has adapted Nabaztag to recognize speech as well.

The field has now settled into two main traditions of research on how to produce machine conversationalists. Both schools take successful work on speech engineering, with data derived from recorded conversations (often on the phone), and seek to derive structures and rules to manage machine dialogs. One, represented by researchers like Steve Young at Cambridge University, assumes that machine learning methods from speech processing can be trained to manage dialogs directly, without intermediate quasi-linguistic structures (*6*). The second follows the route Jelinek later took and tries to recapitulate those linguistic structures but empirically, using machine learning, rather than making up rules, as linguists traditionally did (*7*).

Those in the latter camp currently believe that the infor-

The author is in the Department of Computer Science, University of Sheffield, Sheffield S1 4DP, UK. E-mail: y.wilks@dcs.shef.ac.uk

mation required to automatically transcribe speech to written text is simply insufficient for the larger task of creating a machine conversationalist that "understands." For example, if someone says something that contradicts his or her earlier statement, we would expect a plausible machine conversationalist to spot it. Without some structure and memory, however, it is hard to see how a system could check statements for consistency. One could never expect to learn to do that simply from data: We just do not see or hear enough sentences to have previously encountered all the inconsistencies that we could spot immediately.

At the moment, people encounter machine conversationalists only in recreational chatbots on the Web, or in simple phone transactions such as ordering travel tickets. But research systems are already much better than that, and the range of projects expected to deliver usable prototypes has expanded in recent years. These efforts range from the Defense Advanced Research Projects Agency's Cognitive Assistant that Learns and Organizes project (*8*) to the European Commission's new Companions project (*9*) to create a long-term conversational partner (see the figure). Such a Companion would learn its person's likes and dislikes, carry out Web-related tasks accordingly, and prompt reminiscences about the person's photo collection so as to build up his or her life story through conversation (*10*).

Researchers generally agree that although these large goals need more research, speech recognition technology is still not accurate enough to build a reliable machine partner capable of understanding what we say, unless it has a considerable amount of stored knowledge to enable it to understand; mere reactive chatbots will be no more help than ELIZA was. The current paradigm split in research is about how it will be possible to capture and store knowledge and language experience in large enough detail and volume to build such assistants, outside of very small domains such as recording a complicated pizza order. A long-term assistant to an astronaut on a voyage to another planet, or one to help elderly people recover their past through conversation and organize it in text and images, is a much larger goal, and one that will require better machine learning techniques than have been deployed so far.

The crux of the current research issue is this: Will a successful technology end up recreating by means of automated learning much of the linguistic and logical content that was abandoned in the 1990s? That might be closer to what our own cognitive structures seem to be. In any case, language data will remain central, and the World Wide Web has, as an unexpected benefit through chat rooms, provided researchers with potentially infinite resources of data on human conversations.

References and Notes

1. J. Weizenbaum, *Commun. ACM* **9**, 36 (1966).
2. K. M. Colby *et al.*, *Artif. Intell.* **2**, 1 (1972).
3. The worst can drive out the best—in the tape format wars for home video recording during the 1970s and 1980s, VHS won over Betamax.
4. www.celt.sunysb.edu/celtweb/images/Chomsky%20and%20Aronoff%20(Toledo%20Transcript).pdf
5. P. F. Brown *et al.*, *Comp. Linguistics* **16**, 79 (1990).
6. S. Young, paper presented at the International Conference on Speech and Language Processing, 16 to 20 September 2002, Denver.
7. Y. Wilks, N. Webb, A. Setzer, M. Hepple, R. Catizone, in *Recent Advances in Natural Language Processing III*, N. Nicolov, K. Bontcheva, G. Angelova, R. Mitkov, Eds. (Benjamins, Amsterdam, 2005), pp. 111–129.
8. http://caloproject.sri.com/darpa
9. www.companions-project.org
10. Y. Wilks, *Interdiscipl. Sci. Rev.* **30**, 145 (2005).
11. www.nabaztag.com

12. The author's research was sponsored by the European Commission under EC grant IST-FP6-034434 (Companions).

10.1126/science.1148895

PHYSIOLOGY

An Integrative View of Obesity

Comparisons of responses of various cell types to excess nutrients are yielding patterns that may provide insight into the causes and consequences of obesity.

Brent E. Wisse, Francis Kim, Michael W. Schwartz

The World Health Organization estimates that at least 1 in 10 adults worldwide are obese, and in some western countries, a far greater percentage (25% or more) is affected (*1*). Obesity is a serious concern because it increases the risk of cardiovascular disease, type 2 diabetes, and some cancers, among other health problems. The evolution of public health policies and treatment options depends upon an improved understanding of how genetic and environmental factors interact to favor weight gain, and how excessive weight disrupts metabolism. But getting at the causes of obesity and related metabolic disorders is a formidable challenge, in part because so many body systems are affected. Because disturbances in one organ or tissue can compromise the function of several others, separating cause and effect is often difficult. Yet common themes are emerging that may offer a new viewpoint. Among these is the notion that metabolic dysfunction arises from exposure of the body's cells to an excess of nutrients (*2*). A possible extension of this view is that although the cellular consequences of nutrient excess are similar across diverse cell types, the shared nature of the underlying cellular responses can be obscured by the complexity of the events they initiate. In this light, successful identification of shared cellular responses that underlie disease requires a broad and integrative approach that may ultimately reveal more effective obesity treatment strategies.

The authors are in the Department of Medicine, Harborview Medical Center and University of Washington, Seattle, WA 98104, USA. E-mail: mschwart@u.washington.edu

Fundamental to understanding obesity is the fact that, like body temperature, body fat stores are ordinarily maintained within a narrow range through a process called "energy homeostasis." This process involves brain areas that control appetite and energy metabolism, as well as signals that circulate throughout the body, conveying information about the status of body fuel stores. Among the latter are nutrients themselves, such as glucose and free fatty acids, and hormones, such as insulin and leptin (*3*). Specialized neurons in the hypothalamus and other brain areas sense these factors and control both metabolic rate and the desire to eat. When circulating concentrations of these signals decrease due to weight loss, the drive to eat increases and energy expenditure declines, favoring the recovery of depleted fuel stores. Conversely, when food is consumed in amounts that exceed energy requirements, the circulating concentrations of these signals increase. In this way, homeostatic response mechanisms in the brain are poised to protect the body against changes in fat stores or swings in nutrient availability. Thus, obesity does not simply arise from the passive accumulation of excess weight; rather, it involves the active defense of an elevated level of body fat, and deciphering the causes of obesity should take this into account. Certainly, individual genetic makeup may contribute to variations in the capacity to mount these responses, and may explain why some people are protected against weight gain