of glucose on insulin responsiveness in muscle and on insulin secretion from pancreas are well established, the study by Dentin *et al*. is one of the few to examine hyperglycemic effects in liver. Nonetheless, the existence of glucose toxicity raises the intriguing question of whether the cellular signaling pathways responsible for the adverse effects of glucose are the same as those involved in normal glucose signaling.

As extracellular glucose concentration varies, intracellular signaling pathways adjust accordingly. The glucose signaling pathway studied by Dentin *et al.* was originally described as the hexosamine biosynthetic pathway in the liver. This pathway generates uridine diphosphate (UDP)–*N*-acetylglucosamine, a crucial intermediate in the synthesis of the carbohydrate moiety of complex glycoproteins (*4*). In 1991, Marshall and colleagues proposed that this same pathway might respond to persistently elevated extracellular glucose concentration by causing insulin resistance in fat cells, though at that time the mechanism was unknown (*5*). This "hexosamine hypothesis" for the generation of insulin resistance has since been applied to other organs as well as to dysfunctional insulin secretion, and the current favored mechanism is that UDP–*N*-acetylglucosamine drives the enzymatic, O-linked (modification of a hydroxyl group) glycosylation of serine and threonine residues in intracellular proteins (*4, 5*). This posttranslational modification is widely distributed in normal cells, particularly in proteins of the nuclear pore and those associated with chromatin. Dentin *et al*. add to the list of such modified proteins the transcriptional regulatory protein called transducer of regulated cAMP response element–binding protein 2 (TORC2, also known as CRTC2). O-linked glycosylation of CRTC2 activates glucose production in the liver and is an example of how this modification of proteins serves a clear signaling function in controlling metabolism in the liver

In the nucleus, CRTC2 associates with CREB (cyclic AMP response element–binding protein), a transcription factor that activates the expression of genes that control glycolysis and gluconeogenesis (*6*). CRTC2 enhances the transcription of genes encoding proteins critical to gluconeogenesis, in particular the enzyme glucose-6-phosphatase. This enzyme catalyzes the terminal step in glucose production by the liver and is normally negatively regulated by insulin—when insulin concentration is high, total phosphatase concentration is low (*7*). The cellular energy sensor adenosine 5′-monophosphate (AMP)–activated protein kinase also reduces the concentration of glucose-6-phosphatase, but it phosphorylates CRTC2 on serine 171, inducing its translocation to the cytoplasm where it can no longer affect transcription (*8*). Because *N*-acetylglucosamine attaches itself to the same serine that is phosphorylated, glycosylation serves as a switch to prevent the inhibition of CRTC2. The ultimate result is that abnormally high blood sugar concentration activates enzymes designed to release more glucose (*7*) (see the figure).

So, is regulation of CRTC2 by O-linked glycosylation a normal process that becomes maladaptive during states of nutritional excess, or is it wholly pathological, where pure coincidence allows the hexosamine pathway to block phosphorylation? Both alternatives seem unlikely. It is difficult to see why glucose would induce its own synthesis, and it seems improbable that such an elegant control mechanism would evolve by chance without some selective pressure. Perhaps the answer lies in the complexities of liver metabolism, in which viewing glucose consumption and production as two opposing, linear pathways is too simplistic. For example, glucose-6-phosphatase not only serves in the net production of glucose, but also catalyzes the cycle that converts glucose back to glucose-6-phosphate (and back again). Indeed, under at least some conditions, increases in extracellular glucose concentration have been associated with an increase in this cycling rather than a change in net glucose-6-phosphatase flux (*9*). Thus, even important new insights such as those provided by Dentin *et al*. will require more study before we can understand how they integrate into the complex metabolism of an intact organism under normal and pathological conditions.

References

1. R. Dentin, S Hedrick, J. Xie, J. Yates III, M. Montminy, *Science* **319**, 1402 (2008).
2. W. T. Garvey, J. M. Olefsky, J. Griffin, R. F. Hamman, O. G. Kolterman, *Diabetes* **34**, 222 (1985).
3. J. K. Kim *et al.*, *J. Clin. Invest.* **108**, 153 (2001).
4. C. Slawson, M. P. Housley, G. W. Hart, *J. Cell Biochem.* **97**, 71 (2006).
5. S. Marshall, in *Sci. STKE* **2006**, re7 (2006).
6. A. Cheng, A. R. Saltiel, *Bioessays* **28**, 231 (2006)
7. D. Massillon, N. Barzilai, W. Chen, M. Hu, L. Rossetti, *J. Biol. Chem.* **271**, 9871 (1996).
8. D. G. Hardie, S. A. Hawley, J. W. Scott, *J. Physiol. (London)* **574**, 7 (2006).
9. S. Efendic, A. Wajngot, M. Vranić , *Proc. Natl. Acad. Sci. U.S.A.* **82**, 2965 (1985).

10.1126/science.1155915

COMPUTER SCIENCE

Science 2.0

Ben Shneiderman

Traditional scientific methods need to be expanded to deal with complex issues that arise as social systems meet technological innovation.

The growth of the World Wide Web and the spread of cell phones and WiFi continues to reorder whole disciplines and industries. Entrepreneurs, policy-makers, and researchers have recognized that increased collaboration through these socio-technical systems offers compelling opportunities for business, education, national security, and beyond (*1*). It is time for researchers in science to take network collaboration to the next phase and reap the potential intellectual and societal payoffs (*2*–*4*).

Successful scientific collaboratories among genomic researchers, engineering innovations through open-source software, and community-based participation in cultural heritage projects are all early indicators of the transformative nature of collaboration (*5*).

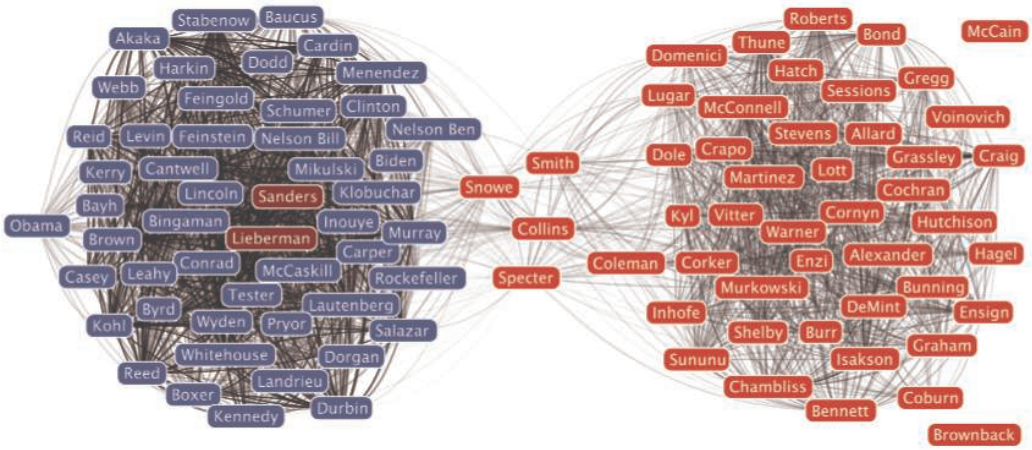
Department of Computer Science, University of Maryland, College Park, MD 20742, USA. E-mail: ben@cs.umd.edu

eBay, Amazon, and Netflix have already reshaped consumer markets, while political participation and citizen journalism are beginning to change civil society. Patient-centered medical information and secure electronic health records are improving health care while creating opportunities for clinical research. MySpace and Facebook encourage casual social networks, but they may soon play more serious roles in facilitating emergency/disaster response (*6*). Social media platforms such as Wikipedia, flickr, and YouTube are also stunning success stories of Web-based contributions.

Understanding these collaboration-centered socio-technical systems could accelerate their adoption and raise their benefits. However, researchers will need to develop new ways of studying these complex interactions. Science 1.0 will continue to be important, but new kinds of science, which I call

Science 2.0, are needed to study the integrated interdisciplinary problems at the heart of socio-technical systems. Science 2.0 will be especially important to meet the design challenges in secure voting, global environmental protection, energy sustainability, and international development among many others.

The guiding strategies of Science 1.0 are still needed for Science 2.0: hypothesis testing, predictive models, and the need for validity, replicability, and generalizability. However, the Science 2.0 challenges cannot be studied adequately in laboratory conditions because controlled experiments do not capture the rich context of Web 2.0 collaboration, where the interaction among variables undermines the validity of reductionist methods (*7*). Moreover, in Science 2.0 the mix of people and technology means that data must be collected in real settings (see the figure). Amazon and Netflix became commercial successes in part because of their frequent evaluations of incremental changes to their Web site design as they monitored user activity and purchases.



Political networking. Collaboration between pairs of U.S. senators is shown by connecting links. The Democratic senators (blue) are at the left and Republican senators (red) at the right; Sanders and Lieberman (magenta) are independents. Brownback and McCain were campaigning for the presidency and did not vote often enough to be linked. Science 2.0 must develop tools like this to analyze human relationships and collaborations (*16*).

Researchers who wish to foster online health care information groups or citizen journalism, for example, need fresh research methods and theories (*8*, *9*). Individual outcomes are difficult enough to study, but understanding why the Google, YouTube, or Facebook communities succeeded in the face of lively competition is still more challenging. These socio-technical systems are best studied at scale, in the real world, by rigorous observations (studying successes and failures), carefully chosen interventions (changing interfaces or privacy rules), and ambitious data collection (analyzing all public user activity). When adequately replicated, these quantitative and qualitative empirical studies can lead to predictive models and effective simulations that guide future designers and researchers.

Science 1.0 heroes such as Galileo, Newton, and Einstein produced key equations that describe the relationships among gravity, electricity, magnetism, and light. By contrast, Science 2.0 leaders are studying trust, empathy, responsibility, and privacy. The great adventure for the next 400 years will be to define, measure, and predict the interaction among these variables so as to accelerate scientific discovery, engineering innovation, e-commerce, and education (*10*). The fivefold growth of research on privacy and trust is apparent in the past 5 years, whereas empathy and responsibility are just beginning to capture attention (*11*).

Science 2.0 researchers are adopting observational and case study methods as they collect quantitative and qualitative data to gain support for their hypotheses about whether trust increases empathy and whether privacy promotes responsibility (*12*, *13*). Their work methods are in harmony with research initiatives on Web science (*14*), creativity support tools, online education (*15*), and socially networked communities, among others.

Advancing Science 2.0 will require a shift in priorities to promote integrative thinking that combines computer science know-how with social science sensitivity. Science 2.0 researchers who develop innovative theories, hypothesis testing based on case study research methods, and new predictive models are likely to lead the way. The quest for empirical validity will drive research beyond what laboratory-based controlled studies can provide, while replicability and generalizability will be achieved with greater effort through multiple case studies. Just as technology-centered researchers measured progress in petabytes of storage or petaflops of processing power, collaboration-centered researchers will measure the growth of peta-collabs of cooperation and peta-contribs of assistance.

Science 1.0 remains vital, but this ambitious vision of Science 2.0 will affect research funding, educational practices, and evaluation of research outcomes. Science funding agencies will face resistance as they promote a transformation that seeks to make a safe space for Science 2.0. Scientific journal editorial boards and conference program committees are already shifting their attention to new topics and opening their doors to new scientific research methods. Pioneering educators have begun changing their curricula, focusing on collaboration strategies and teaching new research methods. The innovators are courageously taking on new challenges, but they should be ready for the resistance to novel ideas that has always been part of science. In that way, Science 2.0 is part of a great tradition.

References and Notes

1. E. Mumford, *Requir. Eng.* **2**, 59 (2000).
2. R. Hiltz, M. Turoff, *The Network Nation* (MIT Press, Cambridge, MA, 1993).
3. B. Shneiderman, *Leonardo's Laptop: Human Needs and the New Computing Technologies* (MIT Press, Cambridge, MA, 2002).
4. W. S. Bainbridge, *Science* **317**, 472 (2007).
5. N. Bos *et al.*, *J. Computer-Mediated Commun.* **12**, 2 (2007).
6. B. Shneiderman, J. Preece, *Science* **315**, 944 (2007).
7. L. A. Suchman, *Plans and Situated Actions: The Problem of Human-Machine Communication* (Cambridge Univ. Press, Cambridge, 1987).
8. D. Maloney-Krichmar, J. Preece, *ACM Trans. Computer-Human Interact.* **12**, 201 (2005).
9. H. T. Welser, E. Gleave, D. Fisher, D., M. Smith, *J. Soc. Struct.* **8**, 2 (2007).
10. G. Fischer, E. Scharff, Y. Ye, in *Social Capital and Information Technology*, M. Huysman, V. Wulf, Eds. (MIT Press, Cambridge, MA, 2004), pp. 355–399.
11. Based on a search of abstracts in the ACM Digital Library: http://portal.acm.org/dl.cfm.
12. R. K. Yin, *Case Study Research: Design and Methods* (Sage, Thousand Oaks, CA, ed. 3, 2003).
13. V. Kaptelinin, B. Nardi, *Acting with Technology: Activity Theory and Interaction Design* (MIT Press, Cambridge, MA, 2006).
14. T. Berners-Lee, W. Hall, J. Hendler, N. Shadbolt, D. J. Weitzner, *Science* **313**, 769 (2006).
15. S. R. Hiltz, R. Goldman, Eds., *Learning Online Together: Research on Asynchronous Learning Networks* (Erlbaum, Mahwah, NJ, 2005).
16. More information about the network diagram including a movie version is available at www.cs.umd.edu/hcil/socialaction.

17. I thank J. Preece, R. Rice, R. Hiltz, M. Smith, G. Fischer, J. Golbeck, and K. Borner for comments.

10.1126/science.1153539