Biologically based dose-response modeling. What is the potential for accurate description of the biological linkages in the applied dose - tissue dose - health effect continuum?

In the game of chess, computers have in recent years become stronger players than the strongest human grandmasters. In some areas of scientific research, for example astrophysics, computer simulations are used to study events, such as the evolution of the universe shortly after the Big Bang, that cannot be studied in the laboratory. In biology, the advent of high throughput "omics" technologies have stimulated development of computational tools that probe the underlying biological structures that gave rise to the data. All of these developments are reflections of Moore's Law, which states that computing power increases exponentially with time, doubling about every two years, and which has proved accurate since it was first proposed in 1965. It is difficult to see with any clarity where computational technologies, including the development of expert systems and artificial intelligence, will lead us in the coming years. What is not difficult to predict is that computation will be integral to scientific research in biology, toxicology, and human health risk assessment. While biology has until recently been a largely intuitive discipline, the future will require formulation of quantitative hypotheses amenable to evaluation in the laboratory and *in silico*. There is no point in arguing about whether or not this should happen. The only relevant questions are exactly how it will happen, and how best to manage and adapt to it. In this presentation these questions will be pursued in the context of dose-response analysis for toxic chemicals. Given knowledge of exposure, the shape of the dose response curve is the key to predicting heath risk, which in turn determines allowable levels of exposure and the associated economic costs of compliance. The public health and billions of dollars are at stake, so it is well worth doing a good job! Specific issues that will be addressed include (1) the state-of-the-art in dosimetry modeling, (2) strategies for computational modeling of complex intra- and intercellular signaling pathways that keep the complexity at a manageable level and (3) use of computational modeling to integrate data collected *in vitro* to provide estimates of risk *in vivo*. *This work has been reviewed by the EPA and approved for publication but does not necessarily reflect the views or policies of the Agency.*