upgrade certain elements of a PC inventory to meet these needs. In addition intranet IO is generally superior to that on the Internet, somewhat reducing application IO limitations.

VS technology is the first family of CAMD applications to see use in a distributed computing environment, because it fits in naturally with the technological demands. The examples described by Davies and Richards focus on the 'more is better' approach in its exploitation. This raises a significant issue, however, because in a typical virtual screen, at least as much time is spent post-processing the results as is in obtaining them [2]. Using today's VS technology with its inherent approximations [3], larger database screens are liable to bring with them larger hit sets with many false positives, making post-screen analysis an increasingly intimidating prospect. If we are to fully harness the potential of distributed computing over the long term, more headway will probably need to be made using the CPU power to run better algorithms, rather than simply running the existing ones faster.

CAMD distributed computing is still in its infancy, with major players in the distributed computing software arena (e.g. entropia: http://www.entropia.com; Platform Computing: http://www.platform.com; and United Devices: http://www.ud.com) continuing to develop code to meet the technological challenges. Further, client side software vendors are still wrestling with the selection of and licensing costs for ported applications in the new environment. Nevertheless, the potential that exists within this computing paradigm is such that it will likely usher in a new and exciting era in CAMD calculations.

References

1 Davies, E.K. and Richards, W.G. (2002) The potential of Internet computing for drug discovery. *Drug Discov. Today* 7, S99–S103

2 Waskowycz, B. *et al.* (2002) Receptor-based screening of very large chemical datasets. In *Rational Approaches to Drug Design*. (Holtje, H-D. and Sipple, W., eds), pp. 372–381, Prous Science

3 Good, A.C. (2001) Structure-based virtual screening protocols. *Curr. Opin. Drug. Discov. Devel.* 4, 301–307

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Systems biology: the new darling of drug discovery?

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Systems biology is gaining momentum. Japan showed great vision in entering the field early, swiftly followed by other countries including the USA, Canada, the UK and, more recently, other European nations such as France and Germany. It is also the new darling of the investment community; reports on systems biology by Cambridge Healthtech Institute (CHI; http://www.healthtech.com) and Frost and Sullivan (http://www.frost.com) emphasize the financial and commercial promise of this new field. But why is systems biology gaining the attention of governments and the financial sector?

Astronomical amounts of genomic and proteomic data coming in from research laboratories lies dormant, not really understood. Systems biology promises to change all that. It attempts to understand the data by integrating it into computational formal theories and models that explain and predict data thereby making sense of it all. Systems biology merges computer science with mathematics, physics and biology. It is a field where interdisciplinary cooperation and research is a defining feature. The *In Silico Biology* conference (part of CHI's *Beyond Genome 2002* triconference; 2–3 June 2002, San Diego, CA, USA) conference displayed the vigor and the promise of this exciting field.

It was a conference not without controversy. There were claims and counter-claims, scepticism and vision, but such are the hallmarks of a burgeoning field. The *In Silico Biology* conference consisted of four sessions: Networks (modeling and cellular networks and pathways), Systems Modeling (modeling whole systems including organs and tissue with the aim of a global integration of networks with data), Cell Modeling (mathematical and computational simulation of

1359-6446/02/$ – see front matter PII: S1359-6446(02)02403-0

whole cells), and Target Prioritization and Drug Development (applying the network, cell and system models to target search and selection as well as assisting the drug discovery process). As we go up the hierarchy from networks, to cells, to systems we lose detail but gain understanding. Each level of abstraction has practical applications to drug development and the search for drug targets.

Network modeling

Integration of data is key to understanding biological processes. Trey Ideker, Whitehead Institute for Biomedical Research (http://www.wi.mit.edu/) kicked off the conference by reporting the construction of a model network of all known molecular interactions in yeast. When such a cellular network is integrated with gene expression profiles, it is possible to explain and predict interactions (generate testable hypotheses) that regulate the observable expression dynamics. That is, we can predict when and explain, in yeast at least, why a gene is turned on and off in response to the state of the network.

Ideker stimulated some controversy, when in the round table discussion, he claimed that the new data and tools made all biological research results and literature older than 10 years obsolete and could be ignored. For this he was firmly criticized by this author for ignoring a century of valuable research results in developmental and cell biology. Indeed, because biological systems are best viewed at different levels of complexity, the data of the past century is just as relevant and valuable today. In the author's opinion it is necessary to integrate that data with the data now being generated.

The universality of all cellular networks was highlighted by Zoltan N. Oltvai, Northwestern University (http://www.northwestern.edu/). He claimed that their recent work demonstrated that the large scale organization of cellular networks appear to be identical in all species, that is, they have the same topology or form. This, he said, puts strong limitations on the possible evolution of all organisms; we might not be able to evolve beyond a certain point. This raises the question: how can we be so different from a frog or a tree when we have the same network topology? One answer could be that a network topology allows for many different instances. A second answer is that there are different categories of networks. The networks Zoltan considers are metabolic networks. If the difference in organisms does not lie there, it most probably arises from differences in the regulatory genomic networks that control the development of organisms.

Collin Hill, Gene Network Sciences (http://www.gnsbiotech.com), discussed ambitious attempts at modeling very large networks and pointed out the need for more computing power as their models of realistic cellular networks and pathways become ever more complex. The aim is to use such models to find drug targets.

Systems modeling

Many of the speakers in the Systems Modeling track emphasized the relevance of systems biology to understanding diseases. For example, Camille Wallwork (Johnson and Johnson; http://www.jnj.com) gave a talk on the uses the Entelos Diabetes PhysioLab to simulate treatment for a form of diabetes. The model has reportedly been helpful in the design and analysis of clinical trials.

Steven Kleinstein, Princeton University, talked about immune response dynamics. He argued for discrete and stochastic models as opposed to differential equations used by others. This was followed by an overview of the systems biology hierarchy by Eric Werner from Cellnomica (http://www.cellnomica.com) who described the company's research in the context of this hierarchy. Databases, genomics and proteomics are near the bottom of the hierarchy. Next come the models of networks and pathways. This being followed by single cell models that integrate networks and pathways with overall cell behavior. At a higher level, others model entire organs through the use of abstracted empirical properties of the tissue. However, although valuable, such models do not integrate intracellular networks with the properties of the organ or its constituents.

Between cell models and whole organ models is an intermediate level, which focuses on multicellular dynamics and development. This requires an integration of cellular networks and signaling pathways with cellular and multicellular processes. Werner argued that many diseases such as cancer are inherently multicellular both in their etiology and phenotype. He mentioned an example of an *in silico* cancer that had many targets that could stop the cancer; however, only two of the targets had minimal side effects. This he argued showed the power of *in silico* analysis in that software and models could save years of research time by showing researchers where to look and how to design their experiments.

In the session on modeling single cells, Douglas Lauffenburger, Massachusetts Institute of Technology (MIT; http://web.mit.edu/), talked of the challenges of modeling cell signaling pathways. Lauffenberger and colleagues use a bioengineering system approach integrating data, models and their dynamics. Similarly, Les Loew, University of Connecticut (http://www.uconn.edu/), presented the Virtual Cell framework. In this framework cells are viewed as containers of interacting biochemical processes that can be mathematically modeled. The framework allows researchers to model chemical reactions as well as to construct two and three-dimensional spatial cell models and then to generate simulations from such integrated models. The effort also aims at setting modeling standards to allow model sharing between scientists.

The problem of using current data with a state model of cell signaling molecules was discussed by Shankar Subramanian, University of California, San Diego (http://www.ucsd.edu). Igor Goryanin, GlaxoSmithKline, gave an overview of the field of whole-cell modeling, and spoke of his group's efforts to model *Escherichia coli* and the potential pharmaceutical applications of this project.

Mathematical models

One of the major differences in opinion of the speakers was what sort of mathematical model to use. Some use differential equations, others use discrete methods, still others use probability theory and statistics and some use hybrid mathematical models combining continuous ordinary differential equations with discrete cellular automata models. To those not familiar with mathematics, it is similar to mixing oil and water; discrete and continuous models are based on different mathematical foundations. However, such a hybrid approach, even if not mathematically clean, might help in understanding complex data. The problem is how to relate the two models in a way that maintains both scientific rigour and the ability to explain and predict phenomena.

In the session on Target Prioritization and Drug Development, Tom Paterson, Entelos (http://www.entelos.com), presented the Virtual Patients framework, which, he claimed, will allow the testing of drugs *in silico* and *in silico* predictions of drug interactions. Bernard Palsson asked a provocative question: What is a pathway for you? The answer illuminated the fact that Entelos seems to have broadened the definition of a pathway by allowing pathways that directly relate low-level molecular interaction with high-level biological phenomena, such as a phenotypic property of a cell or even the effects on the morphology of an organism. This makes it clear that such pathways or networks are hybrid constructions, which is something that mathematical purists might view sceptically. Furthermore, it could make the relationship between the model and the data an *ad hoc* construction. This could lessen if not negate the explanatory and predictive power of the model. By contrast, if done correctly, it could give such models new integrative and predictive power. For sometimes the mathematics has to be developed to fit reality, rather than the other way around.

Christos Hatzis, Silico Insights (http://www.silicoinsights.com/), discussed the problem of integrating data from different levels of organizations. In particular, his company addresses the problem of integrating prior knowledge of genes with experimental measurements of gene expression with the aim of elucidating function. His point was emphasized by several speakers who spoke of the value of preexisting literature on genes in understanding the function of genes and gene expression data.

Summary

Overall the conference showed that systems biology is not only off to a good start but beginning to take off into a promising and exciting future. The movement from wet lab to *in silico* experiments, could not only speed up research and reduce the enormous costs of drug development, they could redefine the very foundations of biology. No longer can a biologist ignore computer science and mathematics. They are becoming an essential component of the field. At the same time the student might benefit if software provides a release from the endless hours, months and years of laboratory work now required to do wet lab experiments. Indeed, the integration of computer science and biology could change our world as much as the computer changed our world in the past century.

Erratum

Please note a correction to the article Tailoring vaccines to individual lymphomas by Matt Brown, published in *Drug Discovery Today*, 1st July 2002, Volume 7, No. 13, 693–694.

We incorrectly stated that a team led by Aaron Rapoport at the University of Maryland had developed the vaccine to treat follicular lymphoma, when in fact the vaccine was invented by Ronald Levy at Stanford University but is being trialed by Rapoport's team against non-Hodgkin's lymphoma.
We would like to apologize for this inaccuracy and for any misunderstanding that this might have caused.

PII: S1359-6446(02)02464-9