Gene Network Sciences Advances Drug Discovery Via Computer Cell Simulations

The pharmaceutical industry's R&D process is excruciatingly slow and staggeringly expensive. Creating a new drug takes approximately 15 years and costs companies upwards of $600 million. With genomics, proteomics, and structural genomics producing more data and more drug targets, the drug bottleneck is only worsening. Ithaca-based Gene Network Sciences (GNS), a leader in systems biology, directly addresses these issues, accelerating drug discovery by leveraging 'omics data (proteomics, metabolomics, structural genomics) to create dynamic computer models of living cells.

By using *in silico* modeling to organize the vast amount of raw data available today, GNS can help companies to prioritize and validate drug targets, saving millions of dollars in development costs, and shortening, by years, the time required to make new drugs.

Founded by two Cornell alumni, Colin Hill and Iya Khalil, GNS retains close ties to the university. Six of the company's 24 employees are Cornell graduates, and several Cornell faculty members are on the GNS Scientific Advisory Board. In addition, GNS is an official partner of the Cornell Nanobiotechnology Center, and the company was co-awarded a NYS Office of Science, Technology, and Academic Research (NYSTAR) grant with Cornell. Hill is the co-founder of Cornell's Computational Cancer Group, a multidisciplinary research effort dedicated to combining computational and experimental approaches to the study of signal transduction pathways.

"Earlier this year, we were faced with the decision of either relocating our headquarters or staying in Ithaca. One major factor in our decision to stay was to maintain our proximity to Cornell and the valuable close relationships we have with many Cornell researchers," says Hill, who serves as the CEO of GNS.

Since its founding in August 2000, the company has made great strides. Last summer, GNS announced that it had created the largest known data-driven computer model of a human cancer cell. The predictive simulation of a colon cancer cell consists of more than 500 genes and proteins responsible for normal cell cycle division, survival, and apoptosis. The milestone was widely recognized in the industry and has been covered by publications including *Nature*, *Wired*, and the *Wall Street Journal*.

The model was built using the GNS Visual Cell™ and Digital Disease Model™ software along with experimental data points of mRNA, protein, and phosphorylated protein levels. The model speeds the drug discovery process by identifying high-value drug targets, testing the efficacy of lead compounds, and running virtual clinical trials.

In building the cancer cell model, GNS overcame two fundamental problems underlying large-scale, dynamical, whole-cell simulations. The first is the ability to concisely represent the detailed molecular interactions underlying a simulation in a manner that is scaleable (to hundreds and thousands of components) and precise enough to be parsed into computer code. The second is "filling in the blanks" for the massive amount of missing biological information related to the precise connectivity of these networks and the kinetic parameters describing the rate of interactions.

To address the scale issue, GNS created the Diagrammatic Cell Language™ (DCL), the first complete language that describes cellular interactions. DCL allows the creation of large-scale models with thousands of components and reactions, and does so in a precise enough way to parse into a mathematical simulation. To infer unknown cell circuitry, GNS created an algorithm that trains the model and constrains unknown parameters, thus accounting for unknown rate constant data.

Other GNS tools (ProbableCell™ and BioMine™) allow for the mining of additional interactions (protein-protein and protein-DNA interactions) not previously found in the literature to enhance the models and account for missing interaction data. GNS then combines all approaches and quantitative time series data into a computational framework called Computational Hypothesis Testing that determines which biological interactions are highly probable and should be verified experimentally.

"Gene Network Sciences has created technologies that are delivering on the promise of a new era in predictive data-driven medicine," says Hill. "We are able to build models with unprecedented levels of detail and diversity of data, allowing researchers to better understand and influence the molecular biology of cancer."

The company is also making progress on the business front. GNS just inked a collaboration agreement with a top-three pharmaceutical company and has also signed licensing agreements providing proprietary modeling tools and software to MIT, the Institute for Systems Biology, and the University of Oklahoma.

In 2002, GNS received two major grants—$100,000 from the National Institutes of Health (NIH) and a $2 million National Institute of Standards and Technology (NIST) award. The company has also raised $2 million in private funding from angel investors and Cornell's BR Venture Fund. Currently, GNS is closing an angel round and is focusing on securing additional collaborations with major pharmaceutical companies.

Colin Hill
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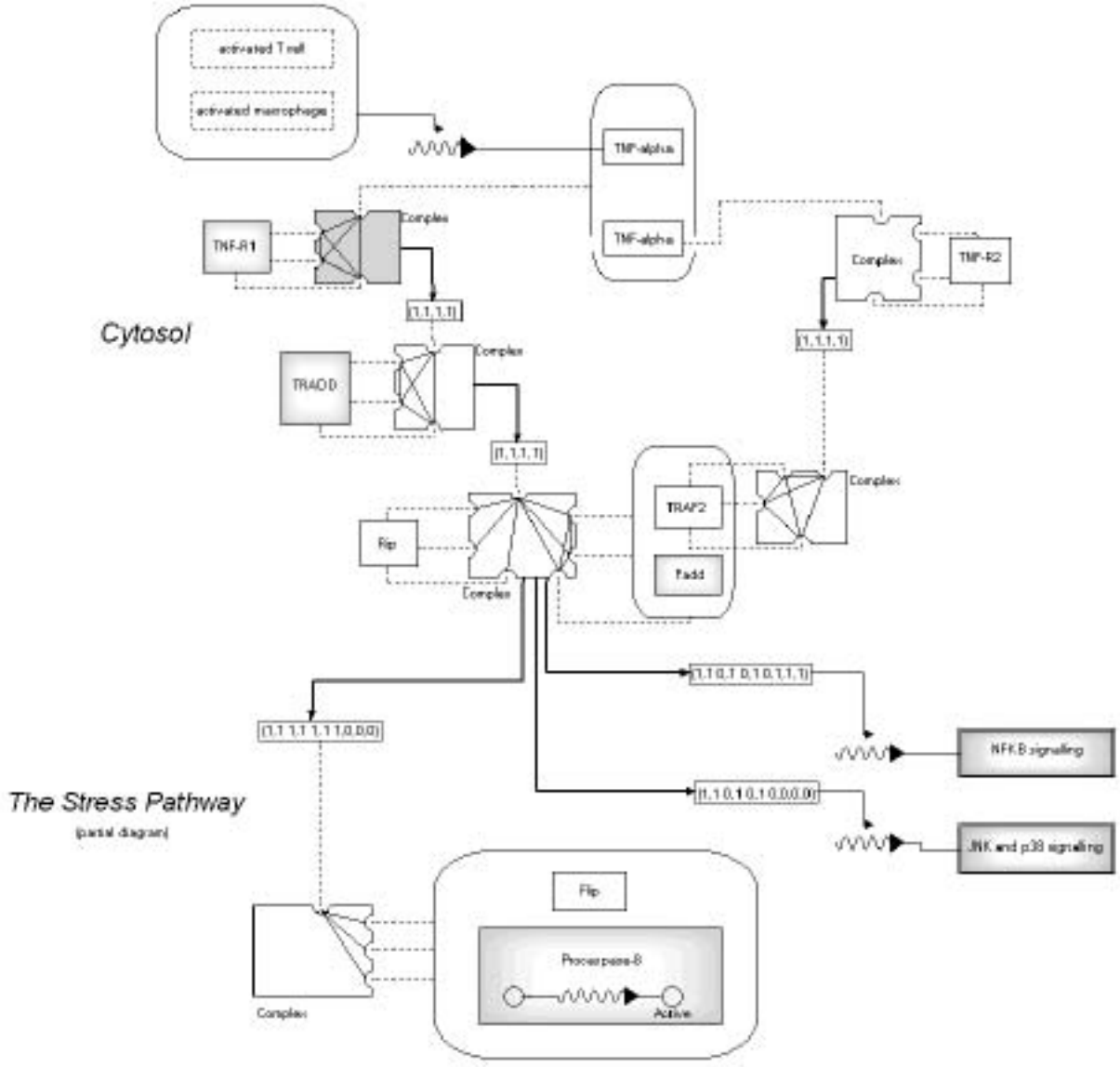
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NFKB signalling
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JNK and p38 signalling
The Stress Pathway
(partial diagram)
Flip
Procaspase-8
Active
Complex

Jon Reis/PHOTOLINK

Colin Hill, CEO
Gene Network Sciences

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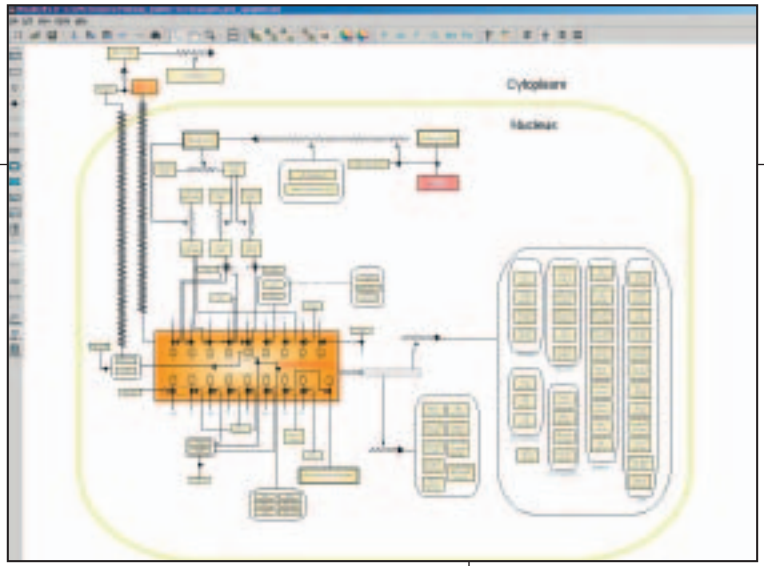
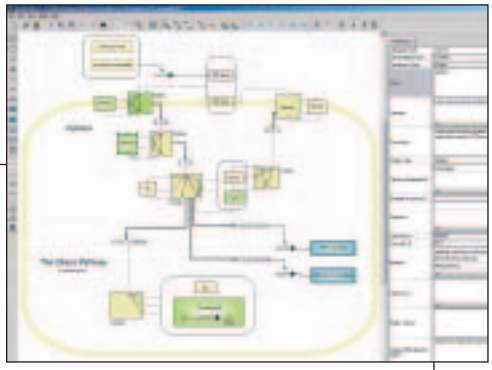
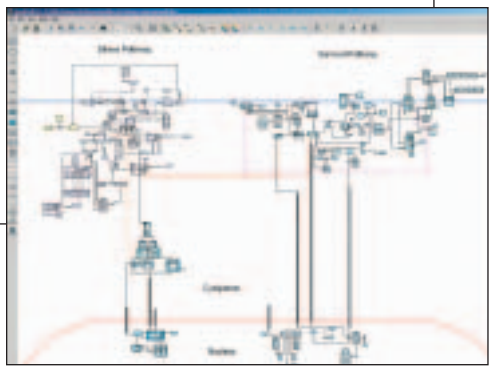
p53 protein modeled using the Diagrammatic Cell Language



p53 inside VisualCell



The stress pathway with annotation



The stress and survival pathways