New models question old assumptions about how many molecules it takes to control cell division

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(PhysOrg.com) -- A single cell - whether a yeast cell or one of your cells - is exquisitely sensitive to its surroundings. It receives input signals, processes the information, makes decisions, and issues commands for making the proper response. As with any control system, noise - errors, slip-ups, mis-reads - can get in the way of correct decision making. Virginia Tech biologists and engineers have created a mathematical model to explore the roles of noise in controlling the basic events of the cell cycle - DNA replication and cell division.

Their work will appear the week of February 23 in the Online Early Edition of the *Proceedings of the National Academy of Sciences* (PNAS) and later in the print version of the special feature issue on complex systems. The article, "Exploring the Roles of Noise in the Eukaryotic Cell Cycle," is by postdoctoral associate Sandip Kar; William Baumann, professor of electrical and computer engineering; Mark Paul, professor of mechanical engineering; and John Tyson, University Distinguished Professor of biological sciences.

Their efforts to accurately calculate the effects of noise in a yeast cell revealed flaws in two accepted notions about information processing in single cells: about the numbers of messenger RNA (mRNA) molecules in a cell, and about how long they live.

A fundamental challenge of systems biology is trying to understand the

molecular basis of decision making in a single cell. "Information processing is done by a molecular network consisting of interacting genes and proteins," Tyson said. "You could compare it to a computer that is based on integrated circuits or to a mechanical control system based on sensors, wires and servomotors -- except that information processing in cells is unique in two ways. First, the cell is a sloppy, liquid environment, with molecules bouncing around and reacting with one another. Second, cells are extremely tiny; therefore sensitive to random fluctuations in the number of molecules being created or destroyed at any given moment."

Nonetheless, the ebb and flow of molecules in a cell must reliably convey instructions for such essential processes as DNA replication and cell division.

How big are the molecular fluctuations expected in a single yeast cell? Physicists estimate molecular fluctuation using a rule-of-thumb that the size of typical fluctuations is the square root of the average number of molecules. "If there are on average 900 molecules of a particular protein in a cell, then we can expect fluctuations of plus or minus 30 molecules, or 3.3 percent," said Tyson. "That is not too bad."

For DNA there might be a severe problem, Tyson noted, "because there is only one copy of every gene in a yeast cell. But cells are equipped with an elaborate and expensive mechanism to replicate DNA molecules and not allow the random fluctuations predicted by statistical physics."

The weak link in the is mRNA: the molecule that carries information from the gene to the cell's ribosomes, where proteins are made.

The literature reports that there is on average only 1 mRNA molecule per gene per cell, in yeast, and that each mRNA molecule lives, on average, for 15 to 20 minutes before it is degraded. "This is intriguing,"

said Tyson, "because the physicist's rule-of-thumb would predict very large fluctuations in mRNA abundance - sometimes 1, sometimes 0, sometimes 2 or 3 or 4 -- which means the noise among mRNA molecules is huge, and it propagates to the level of the encoded protein."

The noisy fluctuations in protein level may be 50 percent instead of 3 percent. "There is no way the control system can work in the face of such large fluctuations," Tyson said. "It would be completely unreliable."

Progression through the cell cycle is indeed a noisy process, with typical flucutations of 15 to 20 percent for the time taken to complete the process. To achieve this level of control, the Virginia Tech researchers conclude, in their PNAS paper, that 1) the average number of specific mRNA molecules must be 5 to 10 times larger than the generally accepted value, or 2) the half-life of mRNA molecules must be 10 to 20 times shorter than the reported value, or 3) the cell must have specific mechanisms for noise reduction in its mRNA populations. Or some combination of these strategies.

"At least we have an accurate model that tells where the questions are," Tyson said. "Computational cell biologists address puzzles like this one by building reliable mathematical models, based on basic principles of physics and chemistry, that address the roles of noise and noise reduction mechanisms in living cells."

Tyson, Baumann, and Paul are lead investigators on an NIH National Institute of General Medical Sciences funded research project that also includes Yang Cao, assistant professor; Cliff Shaffer, professor; Layne Watson, professor; and Adrian Sandu, associate professor, all of Virginia Tech's computer science department in the College of Engineering.

The group is continuing to build more elaborate and accurate models of molecular noise in the cell cycle control system of yeast cells and to

compare these models to the latest experimental measurements of molecular fluctuations in single cells.

Source: Virginia Tech