

Modeling Individual Cell Variability to Improve Quantitative Measurements in Cell-Based Assays

NIST has developed a simple model to predict the highly-robust distribution of responses observed in populations of genetically identical cells that constitutively express different levels of green fluorescence protein in genetic reporter assays. This distribution can be explained by the population response to growth and cell division. The new model is expected to result in improvements for quality control of growing cell cultures and new innovations in drug discovery and development efforts in U.S. pharmaceutical and biopharmaceutical companies.

J. T. Elliott, M. Halter, A. L. Plant (Div. 831)

One of the major goals of systems biology is to understand and predict cellular responses to extracellular signals present in the cell's local environment. Many biochemical techniques, such as Western blots, measure an average result by combining many cells for analysis. When cell-by-cell data are collected, it can be seen that there is a range of responses within the population of cells; although genetically identical, each cell does not display the same phenotype. By careful control of experimental conditions, it can be confirmed that this distribution is highly reproducible and is not the result of experimental noise. Although it is not frequently recognized, the observed distributions in response are due to fluctuations, or noise, in the intracellular processes that are responsible for the cell's response. Without adequate models to describe the origin of this distribution, the observed data obtained in an experiment can be ambiguous.

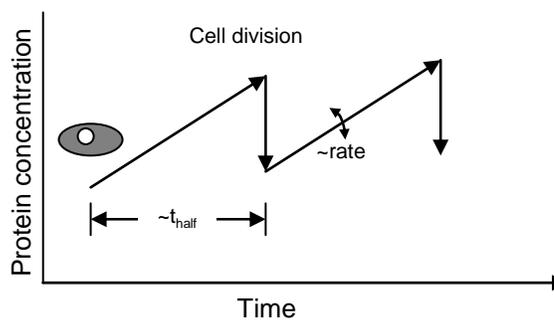
Observing a population of genetically identical cells that are expressing constitutively produced green fluorescence protein shows that different cells exhibit different levels of fluorescence. Any one cell does not experience the entire range of fluorescence intensities within the population; furthermore the distribution is highly robust from experiment to experiment. We have developed a simple model to predict the source of this distribution of these responses, and found that it can be explained by the population response to growth and cell division.

NIST's new cell status distribution model will enable better cell-based assay measurements in drug discovery research.

Data were collected on an asynchronous population of individual cells by flow cytometry. The model is based on a simple dynamical linear-growth and division process where the rate of growth and the division time for each cell cycle is randomly selected from a Gaussian distribution around a mean value, and allows us to predict, based on cell volumes, the average rate of cell growth, and the noise in that rate across the population, and the average time of cell division, and the noise in that time. We find that the mean value and the width of the observed distribution are a function of only the mean growth rate and mean division time for the cell population, and the shape of the observed distribution is a function of the variations in the growth rate and division time. This model provides insight into the biological mechanisms that are governing protein production and cell cycle time.

Our results indicate that any cell-by-cell measurement of a growing cell population will contain noise due to the cell division process (i.e. extrinsic noise) in addition to noise associated with the parameter being investigated. Our fitting procedure will facilitate extracting relevant parameters from observed distributions and quantifying the biological noise that is inherent in cell signaling pathways.

a. Model for linear growth and division of cells



b. Observed and fitted cell-by-cell data

