## Dynamic control and model inference of signal activated gene regulation

GREGOR NEUERT, Vanderbilt University

Despite robust efforts over the years, it has proven very difficult to identify mathematical models that would improve biological insight by predicting complex biological responses, as needed to accelerate the design of medical treatments. This problem remains unsolved because large-scale models, with hundreds of unknown reaction rates, may be too complex to be supported by existing experimental techniques or data sets, and therefore provide little quantitative insight. At the other extreme, overly simple models ignore the intricacies of real biological processes and are equally limited in their ability to predict real phenomena. Models are often further limited by the fact that most experimental analyses only probe average equilibrium characteristics of cell populations and ignore potentially useful information contained in measurable fluctuations in space, time and environment, and from one cell to another. This is a fundamental problem in all of biology, because models and parameters that are identified from measurements of population of cells do not capture the variability in biological processes and therefore these models are profoundly misleading. In essence, models inferred from population averages can fit the population data very well but they cannot predict. The key to overcoming these limitations is to generate single-cell and single-molecule experimental data sets of high quality and reproducibility that capture the variability in biological processes [1-3]. Because single-cell data contain information hidden in population averages, our cellular systems identification methodology of integrating quantitative single-cell experiments with stochastic mathematical models is maximally predictive [3-7]. Our approach is very broad and may be applied to any measurement that detects variability and any biological process that exhibits variability. [1] van Werven, Neuert, et al., Cell, 150 (6), 1170–1181, 2012. [2] Bumgarner, Neuert, et al., Molecular Cell, 45 (4), 470-482, 2012. [3] Neuert, Munsky, et al., Science, 339(6119):584–587, 2013. [4] Munsky, Neuert, et al., Science, 336(6078):183–187, 2012. [5] Munsky, Neuert. Physical Biology, 12(4):045004, 2015. [6] Munsky, Fox, Neuert. Methods, 85:12–21, 2015. [7] Fox, Neuert, Munsky, The Journal of chemical physics, 145(7). 074101, 2016.