Bimodal Protein Distributions in Heterogeneous Oscillating Systems

Maciej Dobrzyński, Dirk Fey, Lan K. Nguyen, and Boris N. Kholodenko

Systems Biology Ireland,
University College Dublin, Belfield, Dublin 4, Ireland
{maciej.dobrzynski,dirk.fey,lan.nguyen,boris.kholodenko}@ucd.ie

Abstract. Bimodal distributions of protein activities in signaling systems are often interpreted as indicators of underlying switch-like responses and bistable dynamics. We investigate the emergence of bimodal protein distributions by analyzing a less appreciated mechanism: oscillating signaling systems with varying amplitude, phase and frequency due to cell-to-cell variability. We support our analysis by analytical derivations for basic oscillators and numerical simulations of a signaling cascade, which displays sustained oscillations in protein activities. Importantly, we show that the time to reach the bimodal distribution depends on the magnitude of cell-to-cell variability. We quantify this time using the Kullback-Leibler divergence. The implications of our findings for single-cell experiments are discussed.

Keywords: signaling networks, oscillations, bimodality, stochasticity, protein distributions.

1 Introduction

Protein levels in cellular systems undergo constant changes due to varying extra- and intracellular cues that are dynamically processed by cellular machinery as well as due to thermal noise – an inevitable factor affecting all biochemical reactions. It is because of this variability that cells within a population, be it a bacterial colony or tumor cells, at any given point in time exhibit a distribution of values rather than a precise value of concentrations of its biochemical components, such as proteins or mRNA. Such distributions can be assessed as population snapshots in fluorescence-activated assays using flow cytometry or cell imaging. In both cases the measurement of fluorescence intensity in individual cells correlates with protein abundance. This starkly contrasts to bulk measurements such as Western blots where proteins are detected in cell lysates, which only estimates the average (per-cell) concentration of the entire population.

Of particular interest are bimodal protein distributions that indicate a temporal or steady-state phenotypic division of an isogenic cellular population. Bimodality often reflects the existence of two subpopulations, each capable of performing a different task [2] or having an altered survival rate to stress [3] and

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drug treatment [15]. Bimodal distributions may arise in a number of situations: a purely stochastic genetic switch [1], a bistable system with stochastically induced transitions [11], or noisy networks with sigmoidal response function [8,9]. In this paper we address a much less appreciated mechanism: heterogeneous oscillations. We show that cell-to-cell variability in protein abundances can result in bimodal distributions of concentrations of active (e.g. phosphorylated) protein forms, although individual cells display solely deterministic oscillatory dynamics. We examine analytically and numerically conditions under which this phenomenon occurs.

2 Results

A *single* oscillating cell visits all intermediate levels between the low and the high protein concentrations. A histogram, or a distribution, of concentrations assumed over time can be constructed in the following manner. The range of concentrations between oscillation extrema is divided into infinitesimally small bins and the time the system spends in each of the bins is recorded. For deterministic oscillations, a single period suffices to obtain such a distribution. Depending on the shape of these oscillations, a bimodal single-cell time-averaged histogram of concentrations may arise (Fig. 1). The key question, however, is whether in the presence of cell-to-cell variability which affects the amplitude, phase and frequency of oscillations in individual cells, the described mechanism can also evoke bimodality at the level of a cellular population? The question is equivalent to asking about the ergodicity of such a system: does the distribution of a population coincide with the distribution of an individual measured over time? The disparity of the two has been recently demonstrated experimentally for noisy cellular systems [14]. Protein fluctuations that are high in amplitude and slow compared to cells lifetime may drive a number of cells to a range of concentrations that is only a fraction of the entire concentration spectrum. This condition may persist well over a cells generation thus rendering snapshots of the population incapable of reflecting the underlying network dynamics.

Similar phenomenon may affect a population of oscillating cells. Even though our analysis focuses on oscillations that are deterministic in individual cells, biochemical noise manifests itself in cell-to-cell variability. As a result, oscillations across the population differ in the amplitude, phase and frequency. If this variability is not large enough, a population might not cover the entire concentration spectrum at a given point in time, and a bimodal distribution fails to emerge. An additional condition is required to facilitate this emergence and relates to a so-called mixing time – the time after which all individuals within the population of cells assume all states of the asymptotic (stationary) protein distribution. We therefore set out to answer following questions: (1) under what biochemical circumstances can a heterogeneous population of cells exhibiting oscillatory dynamics give rise to bimodal protein distributions? (2) What is the time after stimulus required to reach a time-independent bimodal distribution?