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Identifying noise sources governing cell-to-cell variability

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Abstract

Phenotypic differences often occur even in clonal cell populations. Many potential sources of such variation have been identified, from biophysical rate variance intrinsic to all chemical processes to asymmetric division of molecular components extrinsic to any particular signaling pathway. Identifying the sources of phenotypic variation and quantifying their contributions to cell fate variation is not possible without accurate single cell data. By combining such data with mathematical models of potential noise sources it is possible to characterize the impact of varying levels of each noise source and identify which sources of variation best explain the experimental observations. The mathematical framework of information theory provides metrics of the impact of noise on the reliability of a cell to sense its environment. While the presence of noise in a single cellular system reduces the reliability of signal transduction its impact on a population of varied single cells remains unclear.

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Introduction

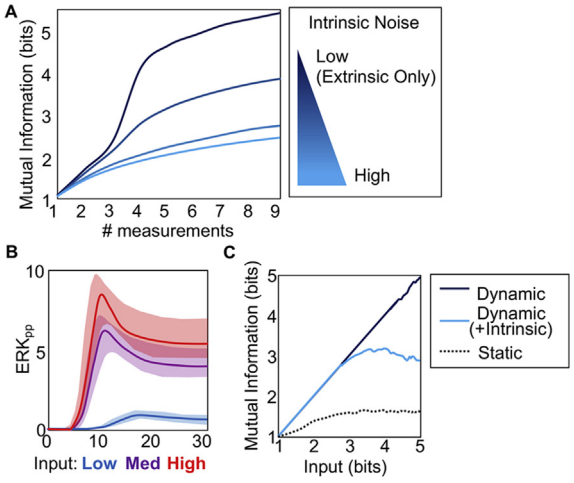
Cells must reliably sense their environment in order to behave and respond appropriately. Sources of information in the environment are highly varied and can include nutrient availability, cytokine and chemokine levels, pathogens and combinations thereof. Sensing the cellular environment typically involves receptor activation and transduction of receptor state information through a signaling network resulting in an appropriate response. Such responses can take the form of gene expression [1], or cell fate decisions such as differentiation [2], division and death [3•]. Mechanistic computational models of signaling networks are valuable tools to explain how a cell can respond to environmental cues with stimulus specific gene expression [4], differentiation [5,6], division [7] and death [3,8].

However, single cell studies have revealed a high degree of variability in the responses of genetically identical cells grown and treated in identical conditions. Numerous theoretical and experimental studies have addressed the sources and physiological consequence of this variability [9–11]. A useful distinction is whether the source of the variability is intrinsic or extrinsic to the regulatory system and timescale being considered. That distinction has indeed important implications to both the biology and our study of it. As intrinsic molecular variability reflects thermodynamic noise of molecular interactions within the regulatory network, modeling, it requires stochastic mathematical representation (e.g. Gillespie formalisms), and may limit the predictability of biological phenotypes, or reliability of signal transduction (Figure 1A). In contrast, extrinsic noise reflects distinct starting conditions (initial concentrations and/or kinetic rate constants) of the molecular networks of individual cells within the population, or distinct time-dependent inputs (changes in the environment) to the system [12,13]. In principle, biological outcomes that are only subject to extrinsic noise can be predicted and modeled with deterministic mathematical formalisms (e.g. ordinary differential equations) so long as the starting conditions and inputs to the system are known. Further, information loss through extrinsic noise can be mitigated through a Dynamical Signaling Code [14,15]. By leveraging information contained in time trajectories, the reliability of signaling is not diminished by extrinsic noise (Figure 1B and C) [16,17].

In a seminal study, an engineered bacterial system was developed to quantify the contribution of extrinsic and intrinsic noise sources to the expression of identical duplicate reporter genes [18]. However, such elegant engineering of signaling systems is not possible in many biological contexts such as the immune system [19,20]. For natural biological systems computational models can provide a tool to elucidate how different sources of variability can result in distinct phenotypes.

Here we will describe how recent advances in single-cell imaging, combined with computational models enable

Figure 1



Dynamic information can increase channel capacity and overcome extrinsic variability [16]. A) Mutual information (the information carried by a channel) calculated as a function of the number of input measurements integrated and the level of intrinsic noise. By integrating multiple measurements from a dynamic input mutual information can be increased to overcome pre-existing cell-to-cell variability. Increasing intrinsic noise reduces the mutual information and cannot be overcome by integrating more measurements of the same biochemical species. B) Trajectories from a computational model of ERK activity show highly variable responses [17]. C) Line graph of mutual information showing that a static single-timepoint measurement is incapable of encoding high mutual information. Dynamic information encoded by integrating measurements from multiple time points can overcome pre-existing variability to achieve high mutual information, this is limited by intrinsic noise.

disentangling the sources and impact of variability on a cell responding to its environment.

Non-genetic origins of cell-to-cell variability in TRAIL-induced apoptosis

Cell death decision pathways are well-suited for investigations into the molecular basis of cell fate heterogeneity due to the distinct and unambiguous phenotype. TNF-related apoptosis-inducing ligand (TRAIL) induces apoptosis through the TRAIL-receptor which activates initiator caspases (caspase-8 and caspase-10) followed by activation of effector caspase (caspase-3) either directly or via mitochondrial outer membrane permeabilization (MOMP) [8]. In response to a fixed dose of TRAIL, a wide distribution of death times is observed within clonal cell populations. By recording and tracking division events that occurred prior to administration of TRAIL a strong correlation between the death times of recently divided sibling cells was found. This indicated the predominance of extrinsic variability present prior to the treatment as substantial intrinsic noise would manifest as a poor correlation between siblings (Figure 2A). Further, by measuring the decay of concordance of death times among siblings as time after division increased, the investigators could quantify the effect of intrinsic noise (Figure 2B). The prevalence of pre-existing extrinsic variability over intrinsic noise motivated the search for determinants of death time in individual cells.

A computational model trained on live-cell imaging and flow cytometry data could recapitulate observed cell-death responses to TRAIL [21]. By incorporating experimentally determined distributed abundance of molecular regulators into the computational model, SL Spencer et al. [8] were able to show that cell-to-cell variable steady-state pre-stimulus protein concentrations were sufficient to explain the variable death times. Through the use of fluorescent reporters the investigators found that variability in the signaling network upstream of MOMP accounts for the distribution of death times. While such results show that a cell's pre-stimulus steady state determines its death time in response to TRAIL, no single protein abundance had predictive power over death time in either the model or through fluorescent reporter assays.

A combination of mechanistic modeling and single-cell Fluorescence Resonance Energy Transfer (FRET) by Roux et al. [22••] revealed initiator caspase trajectory variation within a population controls cell death fates. Insight from a simplified computational model of the apoptosis signaling pathway was used to reduce the complex variety of caspase 8 trajectories to a two variable space represented by the initial rate of caspase 8 activation and time of maximal caspase 8 activity. By mapping populations of single cells to this space a boundary could be found that separates cells within a population that survive from those that die. At different doses of TRAIL the fraction of cells on each side of this boundary explain the fraction of cells dying. An important consequence of the predominance of existing cell-to-cell variability within a population is the sensitivity of fractional killing (the proportion of cells undergoing cell death) to ligand dose (Figure 2C). Cells that survive the fractional killing were also found to maintain a pro-survival phenotype to subsequent stimuli [23].

The potential role of pre-existing cell-to-cell heterogeneity in controlling fractional phenotypes within a population is an enticing one. While it is tempting to extrapolate this finding to other biological scenarios it may not be true in other contexts. For example, stochastic decisions-making in lymphocyte proliferation has been long regarded as the process by which distinct fates are achieved.

Single cell lineage tracking enables quantification of intrinsic and extrinsic noise sources in affecting lymphocyte expansion

Snap shot assays at single cell resolution (such as flow-cytometry) have revealed a high degree of cell-to-cell heterogeneity in B lymphocyte proliferation [24].