Nature Reviews Molecular Cell Biology | AOP, published online 12 November 2008; doi:10.1038/nrm2551

CELL SIGNALLING

Range over strength

> …dynamic range might be a better predictor of functional responses than signal strength…

Signalling networks control cellular responses, but how is network activation ultimately converted to the output of a cellular response? Janes and colleagues now present a data-driven computational approach, which involves globally perturbing the measurements that were used to build the model and then quantifying the loss of model accuracy.

The authors used a data-driven model of cytokine-induced apoptosis that correlated 7,980 measurements of signals that are activated following treatment of cells with a death stimulus (tumour necrosis factor (TNF)), together with a survival stimulus, to predict the extent of apoptotic cell death. Furthermore, the model showed that two previously unknown autocrine feedback loops that involve transforming growth factor-α (TGFα) and interleukin-1α were activated after treatment with TNF.

Janes and colleagues then altered the signalling network measurements by computationally manipulating the dynamic range of each molecule, which they define as "the responsiveness of cell outcomes to incremental changes in signal activation". Unexpectedly, when progressively nonlinearized signals with a compressed dynamic range were used to predict stimulus-specific apoptosis, the models worked well until they suddenly failed catastrophically when built with a particular value of compressed data — a point which the authors called a 'model breakpoint'.

Janes and colleagues reasoned that evaluating why the model suddenly fails at the breakpoint could provide context-specific insight into the biology of signalling networks. Indeed, examination of failed signalling-response models led to new predictions about the roles of kinases, such as AKT and extracellular signal-regulated kinase, in TNF-induced apoptosis. For example, early AKT signalling makes an important anti-apoptotic contribution only when cells lack a functional TGFα autocrine circuit. The most accurate model for predicting cell death, and the highest levels of cell death that the authors subsequently observed experimentally, were seen when the dynamic range of signalling molecules was linearly and uniformly distributed across activation states.

Dynamic range is rarely measured in most signal-transduction studies, because signalling networks are typically measured in either their basal or hyperstimulated states. These new findings, however, suggest that dynamic range might be a better predictor of functional responses than signal strength, and raise the intriguing possibility that signalling networks might evolve to maximize dynamic range.

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ORIGINAL RESEARCH PAPER Janes, K. A. *et al.* Cytokine-induced signaling networks prioritize dynamic range over signal strength. *Cell* **135**, 343–354 (2008)