Abstract for an Invited Paper
for the MAR12 Meeting of
The American Physical Society

Robustness of Biological Circuits

MARC KIRSCHNER, Department of Systems Biology, Harvard Medical School, Boston MA, USA

In responding to inputs biological systems do many types of calculations, some of which serve to maximize the signal and suppress noise. Physiology faces similar requirements and to fulfill these many sensory systems such as vision and hearing are designed to respond logarithmically to the fold change over initial conditions, a property known as "Weber's Law." Mathematical modeling of the ancient Wnt signaling circuit suggested that a key design feature of that pathway was to provide a robust logarithmic output and as a consequence it does not respond robustly in a linear or hyperbolic way. We confirmed this behavior in Xenopus embryos and in human colorectal cells in culture. However, to read a robust logarithmic output from the Wnt pathway in the form of fold change in the levels of beta catenin, the responding transcriptional circuit must be able to compare initial and final levels of beta catenin accurately. This is exactly what we found in Xenopus embryos. What kind of transcriptional pathway has this property? Examination of the detailed promoter of a classic wnt responsive gene showed that two domains contribute to the calculation: the well known TCF/LEF sites that bind beta catenin near the coding sequence and a functional DNA feature upstream, which is unresponsive to beta catenin. The TCF/LEF sites on their own respond in a linear mode to the beta catenin concentration. The upstream functional feature confers the logarithmic response. Knowledge of the pathway structure should allow us to define a "Weber's Law" circuit that allows transcriptional systems to suppress noise by responding to fold change rather than to simple saturation.