Hysteresis in the AKT signaling pathway

"How can unstable molecules stably store information?"

Martin E. Fürst

The starting point

AKT is a protein kinase involved in a number of cellular functions associated with cell growth and proliferation. Usually, its activity is regulated by a number of feedback loops. In many types of cancer, the AKT pathway is not properly down-regulated. Activity of the AKT pathway can be measured by measuring the translocation of FoxO1 to the nucleus. In an experimental study with the novel pathway inhibitor ZSTK, peculiar dose-response curves were measured.

AKT and some of its downstream targets and their respective functions.

Figure from: Manning and Hartley, 2007

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<th>Classical Hysteresis</th>
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<td>( \frac{dN}{dt} = f_{\text{prod}}(N) - f_{\text{dec}}(N) )</td>
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The intersections of productive and decaying influence functions form stable and unstable steady states. Variation of the functions can cause steady states to disappear. Assume e.g. that a stimulus \( S \) is increased from curve a) to d).

In such a case, a system that starts in the state \( N_{\text{low}} \) might suddenly collapse to \( N_{\text{high}} \) and will stay there even after the stimulus returns to its starting value. Such behavior is called "hysteretic".

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The Akt pathway seems to show inverse hysteretic behavior when treated with the drug ZSTK. However, this effect can be canceled by simultaneously applying rapamycin.

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Results / The pathway model

Qualitative flowchart of the AKT pathway. The model contains one negative feedback loop (via mTOR) and one autocatalytic loop (at IRS1). To model the system in a biologically plausible way, Michaelis-Menten enzyme kinetics were added to all interactions sketched above. The resulting "complete" model was simulated in MatLab as a set of ordinary differential equations.

Simulation results are shown above. The curves closely resemble the curves shown in the beginning. The proposed pathway model can explain the observed behavior. It remains to be answered what the minimal model for inverted hysteretic behavior is. Experimental results could be qualitatively reproduced (see below). For quantitative results, probably a biologist is required to do the lab work ;-)