Cell stress response driven by negative feedback: homeostasis and much more

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Living cells use signaling and regulatory mechanisms to adapt to environmental stresses. An ubiquitous feature of stress-response pathways is the role of negative-feedback regulatory loops in maintaining intracellular homeostasis, thereby counteracting and minimizing deleterious effects of stress exposure [1–3]. While the role of negative feedback in contributing to homeostasis can be qualitatively understood from linear response considerations, such feedback motif also mediates a "nonlinear transient response" whose amplitude and duration can strongly impact downstream life- death fate-decision pathways, such as apoptotic or necroptotic responses [4,5]. This issue is first illustrated with experimental and modeling insights of the heat shock response of mammalian cells [6,7]. We then propose a model coupling a negative-feedback 'homeostasis' module with a positive-feedback "loss-of-homeostasis" module to address the impact of transient dynamics on life-death fate decision. Nonlinear dynamical analysis of such low-dimensional model portrays how negative feedback-driven transient dynamics shapes important characteristics of survival curves. We could for instance show how negative feedback characteristics strongly influence (i) the scaling behavior of iso-dose survival curves in the space of stress profile characteristics [8], and (ii) the probabilistic behavior of cell-fate responses by amplifying intrinsic noise [9]. This gives a glimpse of the multifaceted role of feedback-driven nonlinear behavior in cell stress response.

References

1. P. Szekely, H. Sheftel, A. Mayo, U. Alon, Evolutionary tradeoffs between economy and effectiveness in biological homeostasis systems, *PLoS Comput. Biol.*, **9**, e1003163 (2013).
2. H. M. Sauro, Control and regulation of pathways via negative feedback, *J Roy. Soc. Interf.*, **14** 20160848 (2017).
3. E. J. Hancock, J. Ang, A. Papachristodoulou & G. B. Stan, The interplay between feedback and buffering in cellular homeostasis, *Cell Syst.*, **5** 498–508 (2017).
4. M. Metzig, Y. Tang, S. Mitchell, B. Taylor *et al.*, An incoherent feedforward loop interprets NFkB/RelA dynamics to determine TNF-induced necroptosis decisions, *Mol. Syst. Biol.*, **16**, e9677 (2020).
5. J. Roux, M. Hafner, S. Bandara, J. J. Sims *et al.*, Fractional killing arises from cell-to-cell variability in overcoming a caspase activity threshold, *Mol. Syst. Biol.*, **11**, 803 (2015).
6. M. Guilbert, F. Anquez, A. Pruvost, Q. Thommen *et al.*, Protein level variability determines phenotypic heterogeneity in proteotoxic stress response, *FEBS J.*, **287**, 5345–5361 (2020).
7. B. Pfeuty, E. Courtade & Q. Thommen, Fine-tuned control of stress priming and thermotolerance, *Phys. Biol.*, **18**, 04LT02 (2021).
8. D. Labavić, M. T. Ladjimi, Q. Thommen, B. Pfeuty, Scaling laws of cell-fate responses to transient stress, *J. Theor. Biol.*, **478**, 14–25 (2019).
9. J. Hurbain, D. Labavić, Q. Thommen, B. Pfeuty, Theoretical study of the impact of adaptation on cell-fate heterogeneity and fractional killing, *Sci. Rep.*, **10**, 17429 (2020).