Optimal sensory network for the unfolded protein response

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***Short Abstract* —Protein homeostasis requires continuous monitoring of stress in the endolplasmic recticulum. Stress detection networks control protein homeostasis by mitigating the deleterious effects of aberrant protein accumulation, such as excessive unfolded protein, protein aggregates, and misfolded proteins, with precise modulation use of chaperone production. Here, we develop a coarse model of the unfolded protein response in yeast and use multi-objective optimization to determine efficient sensing and activation strategies that optimally balance the trade-off between unfolded protein accumulation and chaperone production.**

***Keywords* — Unfolded protein response, endoplasmic reticulum stress, feedback, Pareto optimization.**

I. Background

THE unfolded protein response is a collection of cellular responses that maintain protein homeostasis in the endoplasmic reticulum (ER) [1,2]. Initiation of the response requires activation of transmembrane proteins that detect the level of stress placed on the folding machinery within the ER lumen. The detection of stress, and activation of the transcriptional responses that mitigate ER stress, are essential to the control of protein folding and malfunction of the ER stress response is related to numerous diseases [3]. At their most basic level, stress detection networks [4,5] act as controllers of protein homeostasis that seek to mitigate the deleterious effects of aberrant protein accumulation, which can lead to aggregation and misfolding, with a precise and efficient use of chaperone production [6]. Aberrant protein accumulation leads to protein misfolding and aggregation of toxic oligomers. Evidence suggests that the response is sensitive to concentrations of both unfolded protein and chaperone in the ER lumen. In this work, we employ a multi-objective optimization algorithm to balance the trade-off between the metabolic cost of chaperone production and the deleterious effects of unfolded protein accumulation in the ER. Using this framework, we analyze a set of biologically-relevant sensory networks that integrate signals from both unfolded protein and chaperone concentrations in the ER lumen to determine underlying rules governing the effectiveness of sensing network designs.

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II. Results

For a sensor that detects the level of unfolded protein directly, we find that the level at which the response is activated dictates the balance of costs, but all costs can be reduced if the magnitude of the response scales gradually with the strength of the stimulus. Additionally, we show that a sensing mechanism that responds to the level of free chaperone in the ER offers more efficient control than sensors that detect unfolded proteins directly. This is the result of the chaperone-detection mechanism having asymmetric activation and deactivation thresholds. Lastly, we demonstrate that a sensor whose activation requires a combination of unfolded protein and free chaperone provides an extra degree of freedom that the cell can use to further optimize homeostatic control.

III. Conclusions

Our results suggest a strategy for the optimal design of stress sensors and provide a possible explanation as to why BiP-mitigated ER stress sensing networks have evolved. By unraveling the different factors regulating the control of the ER stress sensor, our approach can guide the design of homeostatic controllers in other biological contexts as well as synthetic biology.

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