Information transmission and adaptivity in ER stress sensing

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***Short Abstract* — Although significant progress has been made toward understanding the cellular response to endoplasmic reticulum (ER) stress, the precise mechanism by which the cell detects the stress level in the ER lumen remains unclear. Using stochastic rule-based models of proposed sensory networks, we show that an allosteric mechanism that senses ER protein activity levels indirectly through the chaperone BiP is optimal in terms of information transmission. Additionally, this mechanism is self-calibrating is the sense that is detects the stress level relative to the current ER processing capcity.**

***Keywords* — Endoplasmic reticulum, stress, cell signaling, rule-based modeling.**

I. Background

THE unfolded protein response (UPR) is a cellular stress response resulting from excessive accumulation of unfolded and misfolded protein in the endoplasmic reticulum (ER). Detection of heightened protein concentration within the ER lumen triggers accelerated protein folding and degradation within the ER along with decreased protein synthesis. Malfunction of the UPR has been implicated in numerous protein misfolding diseases [1], including type II diabetes mellitus [2]. Although significant progress has been made toward understanding the downstream cascade regulating chaperone production and ER-associated degradation (ERAD), the actual molecular mechanism through which protein load in the ER is detected has remained controversial [3,4]. In this work, we evaluate the canonical mechanisms proposed for ER stress sensing with regard to their capacity to transmit information and their adaptivity to changes in the basal processing capacity of the ER.

II. Results

Using rule-based stochastic models [5,6] of three candidate reaction mechanisms, we simulate their responses to varying degrees of ER stress. In the first numerical experiment, we compare a direct sensing mechanism, in which unfolded proteins act as ligands for the transmembrane receptor Ire1, with an indirect mechanism, in which the chaperone BiP binds competitively to unfolded proteins and Ire1, preventing activation of Ire1 when bound. We show that the indirect mechanism is self-calibrating with respect to the folding capacity of the ER.

Next, we assess the mutual information of the direct, indirect, and a recently-proposed allosteric mechanism [7], in which unfolded proteins directly cause Ire1-bound BiP to release, thereby freeing Ire1 to dimerize and commence downstream signaling. By altering the strength of this allosteric mechanism, we show that the information transmission can be maximized. Furthermore, the allosteric signaling mechanism outperforms both the direct and indirect signaling mechanisms with regard to mutual information.

III. Conclusion

Our results provide a motivation for the evolution of an indirect allosterically-modulated sensing mechanism for ER stress. This mechanism both captures the activity level in ER lumen with the greatest fidelity, and is self-correcting for times of high protein throughput, such as directly following feeding. More generally, the adjustability of the sensing mechanism to variable levels of stress could provide a useful design paradigm for synthetic biologist seeking to construct artificial sensors capable of detecting signals over a variable range of inputs.

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