

1145-92-2954

Laura F Strube* (lfstrube@vt.edu) and **Frederick R Adler** (adler@math.utah.edu). *A Mathematical Model of Translation Regulation by the Integrated Stress Response: the ISR as an Analog-Digital Mechanism Tuned by eIF2B.*

The integrated stress response (ISR) is a conserved pathway that is activated in response to a range of intracellular stress conditions. At its core, this mechanism diverts two central factors from the translation cycle and in doing so attenuates canonical protein translation. Paradoxically this diversion also upregulates expression of stress response genes via a non-canonical translation mechanism. The key players of this system are the translation factor eIF2, its recycler eIF2B, an eIF2 kinase, and the transcription factor ATF4. We describe a non-linear ODE model of ISR-induced translation regulation incorporating probabilistically-derived reaction rates to describe translation as a function of stress level. We show that this model exhibits a range of responses tuned by eIF2B. At one extreme, low eIF2B produces a digital response with small amounts of stress causing a dramatic drop in canonical translation and increase in the expression of ATF4. At the other, high eIF2B produces an analog response in which translation rates change gradually with stress. Intermediate eIF2B concentrations produce a hysteretic hybrid of these two behaviors. This model shows that variation in eIF2B concentration across cell tissues provides a means of tuning the sensitivity of the ISR to stress. (Received September 25, 2018)