**Low stress weekends cannot promote adaptation to stressful weeks: The design principles of the biological response to stress**.

Nilgun Yilmaz, Amsterdam, The Netherlands; Alexey Kolodkin, Seattle, USA/ Luxembourg, EU; Nick Plant, Surrey, UK; Hans Westerhoff, Manchester, UK

Robustness is a fundamental and essential property of evolvable biological systems. It provides system to conserve its functionalities against internal/external perturbations and uncertainties. Product inhibition, feed-forward and feed-back inhibition and stimulation, and regulatory loops within signal transduction networks are a few of the approaches generated by biological systems to maintain both their robustness and adaptability. In this study, we are able to show the interaction of the stress hormone cortisol with its two nuclear receptors, the high affinity glucocorticoid receptor (GR) and the low affinity pregnane X-receptor (PXR) by using a mathematical model based on realistic kinetic parameters. We checked the importance of regulatory loops, within this network, in terms of pharmacodynamic and pharmacokinetic responses. Then, we demonstrate the alterations in the system response with respect to variable cortisol perturbations, such as initial single peak in cortisol, and repeated stimuli of cortisol with differing frequencies and time frames. As a conclusion, we reveal that the network is robust towards low frequency perturbations, shows adaptation at moderate stress frequencies, but transitions to an altered steady state at high frequency stimulation, which we believe is a predisposing factor towards stress-induced pathologies.