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GASTVORTRAG

Die Arbeitsgruppe Numerical Analysis lädt zu folgendem Vortrag ein:

Carlos Lopez
Vanderbilt University, USA

A systems approach to study reaction flux and information flow in an allosteric regulation networks

Cells exist in a state of constant flux, subject to intrinsic and extrinsic perturbations that directly affect the dynamics of biological network processes. These perturbations can disrupt network signal execution in ways that are not easily discernible from experimental approaches, which typically measure network end-points in signal execution. This limited understanding of signaling network mechanisms often leads to an incomplete picture of cellular process execution. This gap in our knowledge is not due to a lack of experimental or modeling efforts, but rather to the complexity associated with signaling flux and information flow in biochemical reaction networks. Here we present a novel approach that combines model exploration, Bayesian calibration, kinetic analysis, and Information Theory approaches to study how information flows in complex biochemical networks. We study the reaction kinetics allosteric modulation of the Cycloxygenase-2 (COX-2) catalytic network, a protein central in inflammation and the target of most NSAIDs to date. Our COX-2 Reaction Model (CORM) describes the dynamics of COX-2 processing arachidonic acid and 2-arachidonyl glycerol into prostaglandin (PG) and prostaglandin-glycerol (PGG). The network was calibrated to experimental data using a Bayesian inference method to determine converged parameter distributions. We analyze the network with a non-equilibrium flux-analysis method to characterize multiple pathways in the network cooperate toward signal processing outcomes that lead to PG or PGG production under different substrate concentrations. Global sensitivity analysis with the products as outputs aligns well with known COX-2 drug efficiencies. However, global sensitivity analysis performed in different regions of the substrate space indicates that the sensitivity of PG and PGG outputs to different perturbations is dependent on initial substrate concentrations. We apply information theory methods to understand the link between biochemical flux and the maximum channel capacity through a given path from reactants to products. Our initial analysis indicates that channel capacity is highly variable within the reaction network and exhibits dependence on the correlation across inputs. Our observations have direct implications for pharmaceutical targeting of COX-2 *in vivo* as well as for other enzyme-substrate systems that exhibit multiple heterogeneous substrate inputs.

Zeit: **Mittwoch, 15. Januar 2020 um 17:00 Uhr**

Ort: **Technikerstraße 13a, HSB 6**

Gäste sind herzlich willkommen!

Lukas Einkemmer