Singapore-MIT Alliance for Research and Technology

BIOSYSTEMS AND MICROMECHANICS

Focused Seminar Series on Computational Techniques

15 Feb — 11 Apr 2016, Level 5 Seminar Room, Enterprise Wing @ UTown, S'138602

Seminar 5: Computational modeling of cell signaling dynamics: Overcoming the tyranny of the receptor

Professor Lisa Tucker-Kellogg

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Date: 14 Mar 2016, Monday
Time: 4pm to 5pm
Venue: Perseverance Room, Enterprise Wing Level 5 @ UTown

Abstract

In the information processing of a cell, external chemical stimuli (e.g., hormones or cytokines) are communicated to intracellular systems through biochemical reaction networks that can be viewed as systems of ordinary differential equations (ODEs) representing changes in concentration over time. Well-studied pathways such as PI3K-Akt, TGFb-Smad, and TRAIL-induced apoptosis have extensive published evidence and accepted enzymatic reactions, which can be used for building such models. Unfortunately, models rarely match reality.

In this work, we view discrepancies between models and reality as starting points for identifying gaps in accepted understanding, and for guiding experiments to delineate novel effects. We present three case studies: (1) In TGF-β1 signaling, the long-term decline of phospho-Smad suggested novel regulation of the PPM1A phosphatase in HaCaT cells. (2) In Akt signalling, a discrepancy between PIP3 dynamics and phospho-Akt in serum stimulated fibroblasts pointed to a novel effect that regulates the membrane translocation of Akt. (3) In TRAIL-induced apoptosis, an anti-cancer drug (LY30) caused caspase-8 activity to increase but with an unexpected delay, which pointed to a non-monotonic effect of LY30 on the apoptosis inhibitor c-FLIP.

In each of these three cases, the conventional expectation (the "textbook" model) would have had intracellular output governed primarily by receptor activation state, but instead we discovered that intermediate levels of regulation were responsible for the observed output dynamics. This work illustrates how computational modelling and wetlab experiments can iterate for mutual benefit.

Biography

Lisa Tucker-Kellogg is an Assistant Professor at the Duke-NUS Medical School in Cancer & Stem Cell Biology (CSCB) and in the Centre for Computational Biology (CCB). Her lab studies wound healing and computational modeling of biochemical pathways. Prior to joining Duke-NUS, she was a Senior Research Fellow at the Mechanobiology Institute Sinagpore, and a Lee Kuan Yew Postdoctoral Fellow (LKY-PDF) at the NUS School of Computing. Originally from the United States, she obtained her Bachelor's degree from Yale and her doctoral degree from MIT, both in Computer Science.