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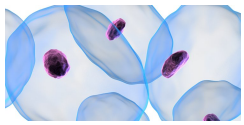

Breaking the NAD+ feedback cycle: how much NAD+ degradation is enough?

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Type of thesis: Computational

Required competences: Ability to analyse and simulate ordinary differential equations (ODEs). Basic knowledge of prokaryotic metabolism would be useful but is not required.

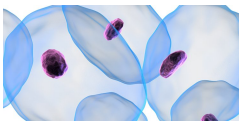
Acquired competences: Ability to analyse data and simulations of mathematical models. Designing experiments to test model predictions.

Date: 25-08-2020

Description

Control of NAD+ (nicotinamide adenine dinucleotide) levels are essential for maintaining cell metabolism in both prokaryotes and eukaryotes. At the most basic level, NAD+ functions as an electron carrier that is essential to central metabolism. However, various proteins including TIR, Sir2, DNA ligase, and phosphotransferases, degrade NAD+. In certain cases, degradation of NAD+ yields ADPR, which mediates downstream signalling in eukaryotes. In humans, this could result in syndromes and diseases that require medical treatment. In prokaryotes, NAD+ degradation could result in cell death and/or cell dormancy. Interestingly, in some circumstances when the NAD+ synthesis or consumption pathways are externally modulated, prokaryotes can adapt to maintain "healthy" levels of NAD+. This suggests that part of the NAD+ network forms a feedback loop that relays information from NAD+ consumption to regulate NAD+ synthesis. We are interested in understanding how this feedback mechanism works and whether rules exist as to how fast cell adaptation is achieved.

In this project, we will look at what levels of NAD+ degradation are maintainable. Using mathematical models and analysis, we want to simulate the NAD+ network given different levels of NADase input to understand how much NAD+ consumption is required



to break the feedback loop and prevent adaptation back towards normal NAD+ levels. This will require the knowledge to construct and simulate ordinary differential equations in MATLAB or Python. We will initially try to find reaction rates from literature sources, or estimate these based on computational methods. Furthermore, by relating our model to NAD+ levels found naturally in *E. coli*, we are interested to see if the model can predict the effects of various experimental conditions, e.g. "pulsed" NADase inputs, that could be tested later in the lab.

References

Olivera, B. M., Hughes, K. T., Cordray, P., & Roth, J. R. (1989). Aspects of NAD Metabolism in Prokaryotes and Eukaryotes. *ADP-Ribose Transfer Reactions*, 353–360.

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