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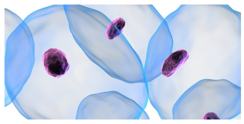

Modelling system-wide effects of temperature on a temperature-sensitive microbial kill switch

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Type of thesis: Computational

Required competences: Mathematical modelling and optimisation as taught in SSB50806, SSB30806, SSB31806 or equivalent. Ability to code in Python also required. Basic knowledge of cell biology also an advantage.

Acquired competences: Model analysis and generating hypotheses from simulations. We may also look at hybrid modelling methods combining mathematical modelling and machine learning.

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Description

As part of the iGEM 2022 competition, synthetic circuits were created that constrained an engineered E. coli to live within specific colon microenvironments (see iGEM reference below). One such mechanism acted as a kill switch, so that the engineered microbes would not survive when exposed to temperatures hotter or colder than body temperature (approximately 37 oC). The production of toxins, represented by fluorescent markers for system development, led to a reduction in growth rate and cell population survival in cooler and warmer temperatures. However, temperature has a global effect on chemical reactions: it is not true that temperature will only effect one part of the circuit, but the production of toxins is the result of temperature regulating all reaction rates (e.g. as measured by Q10 values). Thus, given that chemical reactions tend to speed up with temperature, it is interesting that the kill switch has a temperature optimum in function.

In this project, we will build a mathematical model to work out which parts of the kill switch network are (in)sensitive to temperature and understand the temperature-dependent response of the kill switch in greater detail. Similar modelling strategies have been used for circadian clock systems, whose system-level properties are known to be temperature-insensitive, and we will use this example as an initial basis for our modelling strategy (Gould et al. 2013). If time allows, we may then look to apply physics-informed neural networks to analyse temperature-sensitivity of reaction rates (Rackauckas et al., 2020). By building such a model we will be able to generate hypotheses as to how such a kill switch would function in fluctuating temperature environments, and general rules for all such synthetic circuits.

References

Biosafety, Wageningen iGEM 2022, https://2022.igem.wiki/wageningen-ur/results

Gould PD, et al. (2013) doi: 10.1038/msb.2013.7

Rackauckas C, et al. (2020) doi: 10.48550/arxiv.2001.04385