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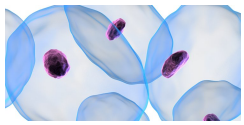

Deriving switch-like sensitivity mechanisms of photoreceptors to their cofactors in optogenetic tools

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Type of thesis: Computational

Required competences: Knowledge of ordinary differential equations (ODEs) and their analysis, ability to simulate systems in MATLAB or Python is desired but not necessary.

Acquired competences: Model development, practical experience of parameter estimation methods, data analysis, basic understanding of photoreceptor biology in natural and synthetic/optogenetic systems.

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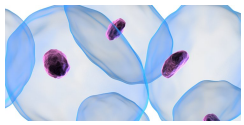
Description

In natural systems, photoreceptors (light regulated proteins) exist in one of two states – a biologically inactive form, and an active form that controls downstream signalling. Generally, the photoreceptor is activated when exposed to light and, due to thermal reversion, relaxes back to its inactive state after prolonged periods of darkness. Phytochromes are a special case of this system whereby they are activated by red light and inactivated both by darkness and exposure to far-red light. This light-inducible switching mechanism has been utilised in several optogenetic tools, whereby the protein variant used has been shown to be thermally stable in darkness.

However, in our hands, we found that the protein variant commonly used in optogenetics does show thermal reversion in vitro. Previously, we have used this to test the effects of protein interactions (namely with PIF6 proteins) on the thermal reversion property of phyB, since complex formation (that would occur naturally for transcriptional purposes or in nuclear speckles) is believed to inhibit this process. Our initial mathematical models of the system supported this hypothesis, however they were unable



to perfectly match the switch-like sensitivity of active phyB to PIF6 concentration (see Figure 3C in the reference).

In this project, I wish to re-evaluate this data from a different angle. Initially ignoring what is known biologically, is it possible to construct a mathematical model of a light regulated system that can explain phyB sensitivity to PIF6 in darkness (after stimulation with red light). From there, once a mechanism has been found, we can ask how this relates to what we know about phytochrome photochemistry and what experiments would be required to prove such a mechanism exists.

References

Smith RW, et al. (2017) Interactions between phyB and PIF proteins alter thermal reversion reactions in vitro. *Photochemistry and Photobiology* **93:** 1525-1531