

Research areas

• Synthetic biology (engineering cells):

- Designing and constructing genetic regulatory networks to be inserted into bacteria and yeast
- Using these networks to exert control over the dynamics of cells, altering their behaviour in controlled ways
- Using constructs to enable experiments on cellular dynamics that would otherwise be difficult to arrange

• Systems biology (understanding cells):

- Fundamentally, biology represents a playing out of chemical and physical laws (though in regimes that are traditionally challenging)
- We formulate mathematical models of processes such as gene expression and regulation, and run experimental tests in actual cells (bacteria and yeast) to compare to our experiments

Our approach

- Combination of experiments and theory/modelling under one roof

- If you want to do both, this is strongly supported (encouraged, in fact): carrying out both the experiments and the modelling is best way to understand a system

- Using modelling/theory/computation **and** a biological bench lets us integrate the perspectives from both sides: it helps keep theory grounded, and helps guide experiment with theoretical insights

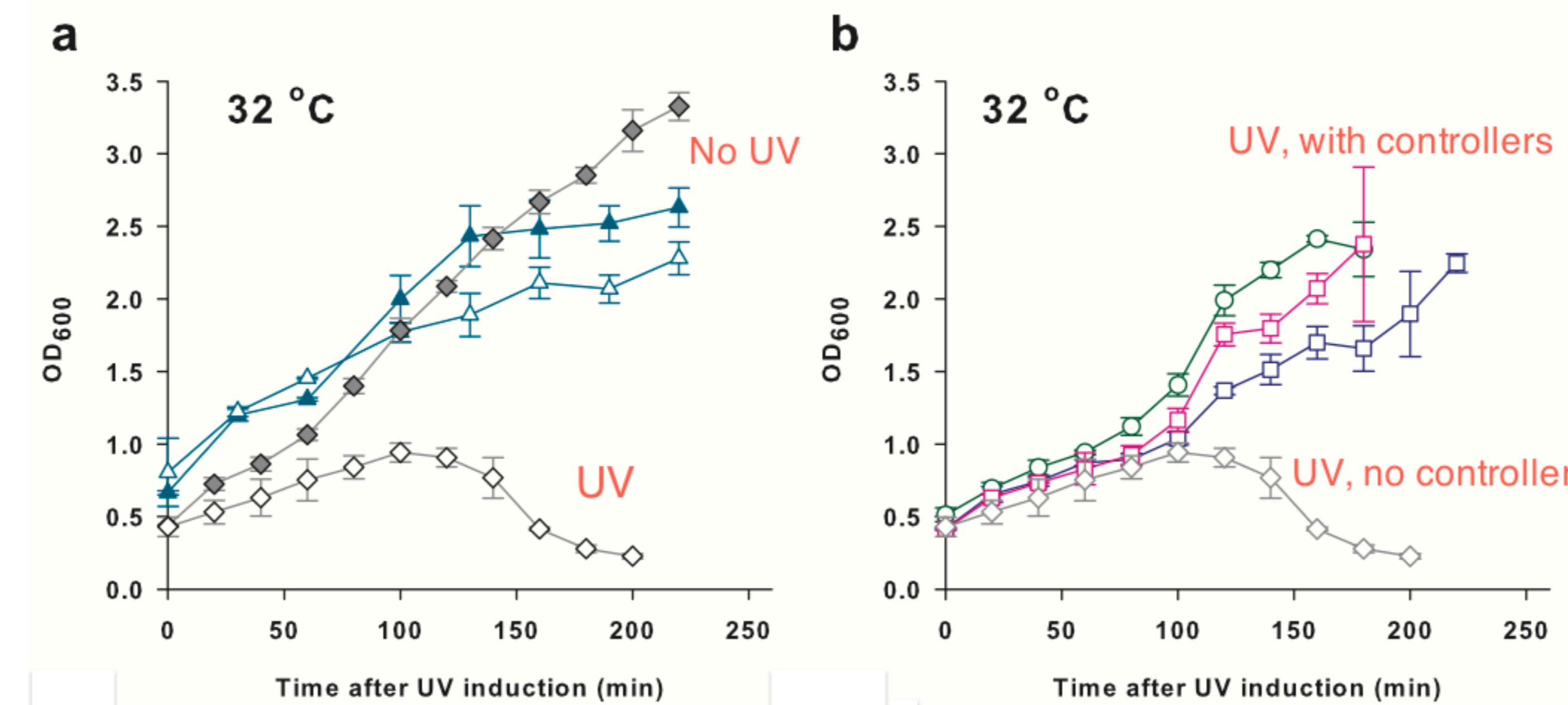
Some ongoing projects

(This isn't everything we're doing, there are other projects. Or start your own! We'll talk.)

Disease prevention

- One goal in synthetic biology is to create devices that can reside inside the cell and detect the onset of disease, then act to cure or mitigate the disease

- **Disease prevention achieved.** We've created such a device, in the case of a bacterial disease: bacteria infected with this virus normally die after exposure to too much UV radiation (it causes the virus to go from a dormant state to one where it replicates rapidly and kills the cell); we have made controllers that detect this switch and act to save the cell. It works!



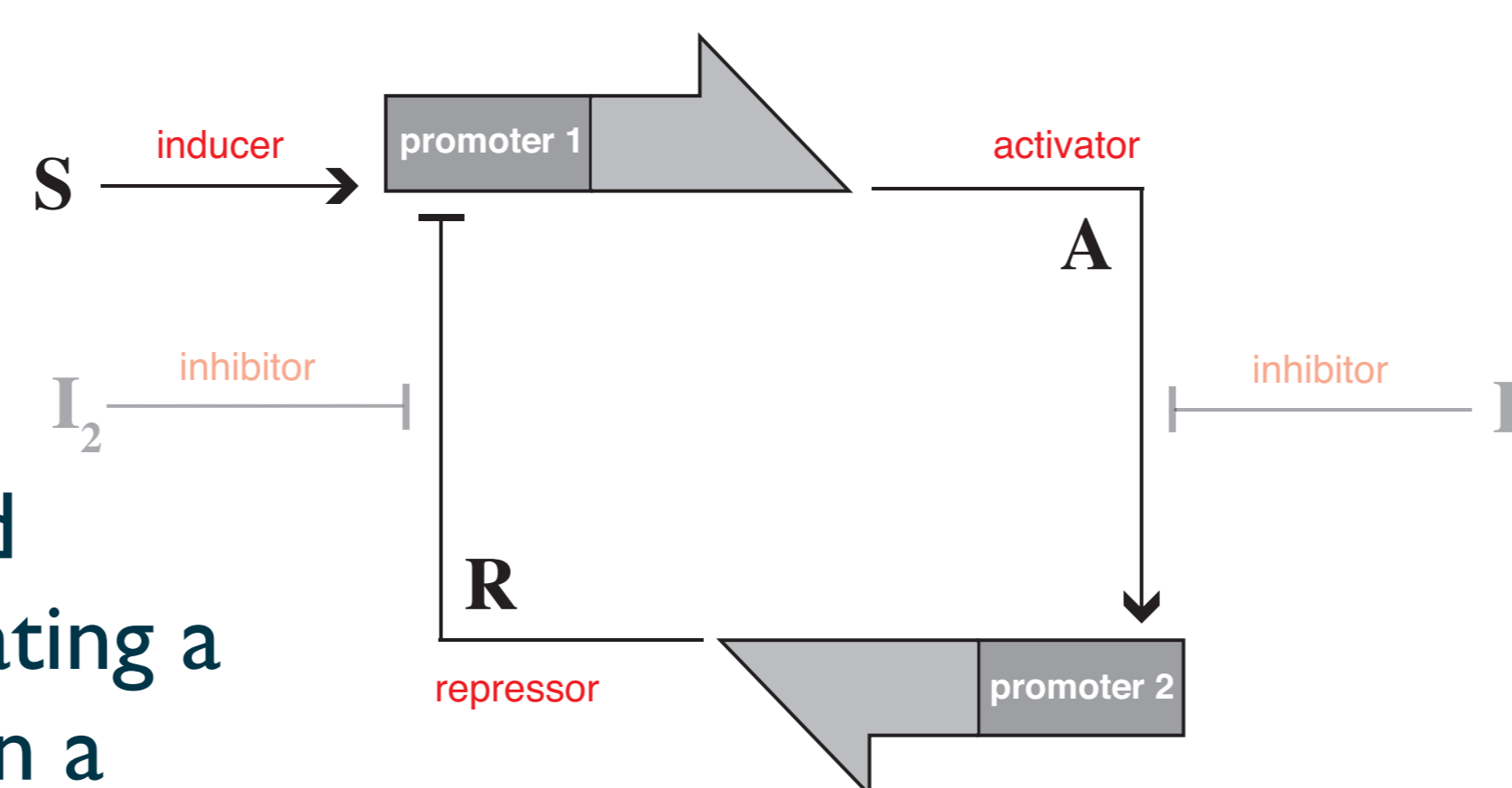
- Future: extend this work to prion disease models in yeast, to mammalian cells, etc.

Coupling switches into yeast cell cycle control

- Yeast regulate their cell division through a complex set of biochemical interactions that have been extensively studied. We are working on a way to incorporate bistable switches (artificial genetic devices that can be “flipped” from one state to another) into the yeast genome, as a method for perturbing and controlling the cell cycle in interesting new ways. These studies may allow us to better understand cell cycle control, with eventual implications for human diseases such as cancer (a disease of cell division).

Integral feedback control

- To maintain a controlled output that's independent of whatever perturbations come along, one needs to use a control approach called integral feedback. We're creating a device that implements this in a synthetic circuit

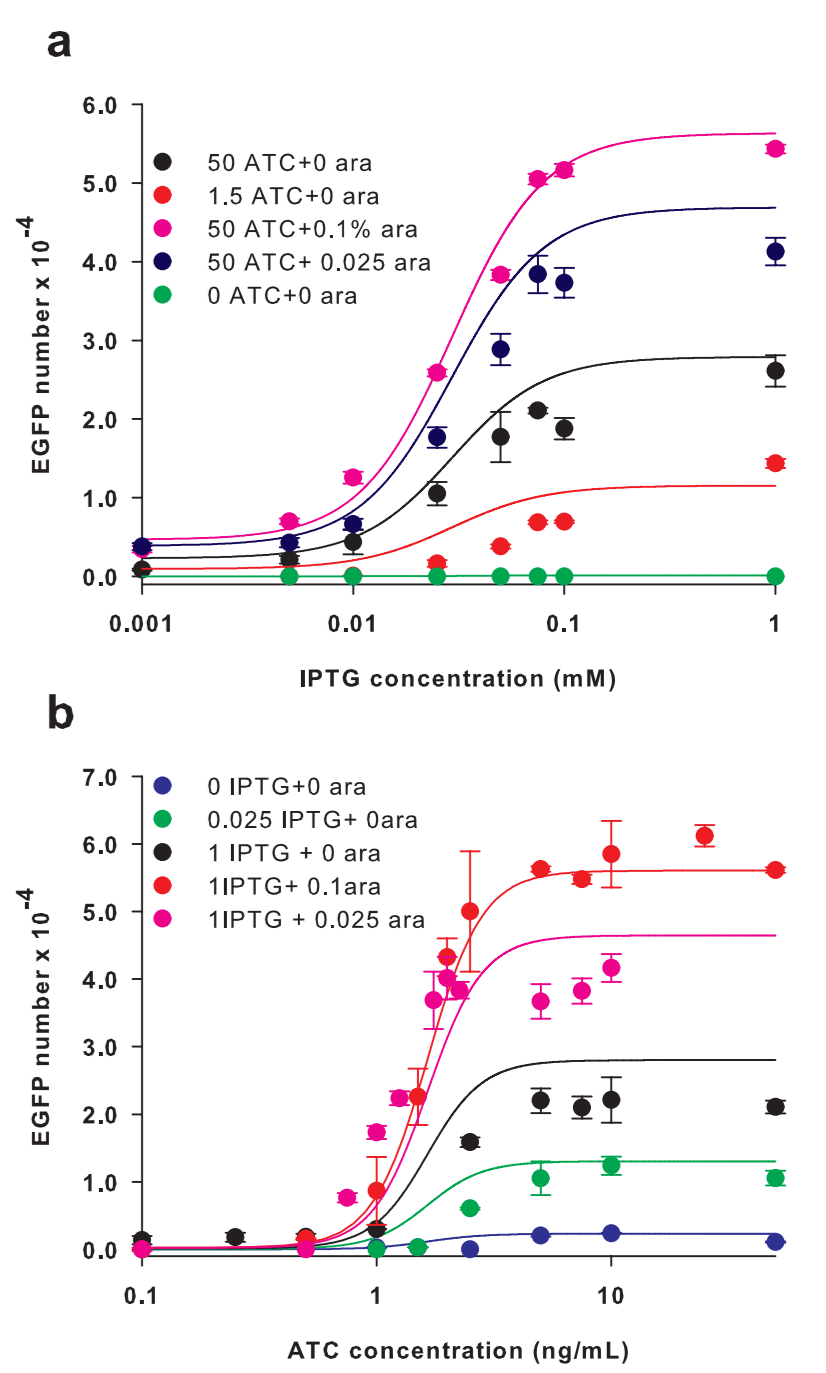


- Modelling work so far, experiments to come

Tunable biological devices

- It's important, when designing devices, to be able to tune their behaviour without re-engineering; genetic alterations to biological devices are especially time-consuming. We have created tunable devices that can alter their behaviour without genetic changes:

- One device changes from a band detector to a sigmoidal response, when the temperature is altered
- Another can implement digital AND logic and a variety of input/output curves in response to chemical inducers



Effects of macromolecular crowding on dynamics

- We often write models of cellular processes using chemical kinetics that apply in relatively dilute solutions, but cells are far from dilute: it's like a thick gel or paste, in there. Nobody knows what effect this should have on our modelling picture of cellular dynamics, and we're carrying out experiments where we systematically add extra crowding agents to an *in vitro* system, to see what it does to the dynamics.

Effects of reporter protein behaviour

- Reporter proteins like GFP are one of our main windows into what's happening inside cells, so we've spent some time studying the relationship between the fluorescence signals they generate and the actual numbers of proteins being produced. Complications include the fact that fluorescent proteins don't start to glow instantly: they go through a maturation process that can take from minutes to days to complete. We've worked out the mathematical details of how this affects one's observations relative to the biological reality.

Recent Publications

- Sangram Bagh and David R. McMillen (2009). A synthetic genetic circuit whose signal-response curve is temperature-tunable from band-detection to sigmoidal behaviour. *Natural Computing* (published online).
- Marco lafolla, Mostafizur Mazumder, Vandit Sardana, Tharsan Velauthapillai, Karanbir Pannu, and David R. McMillen (2008). Dark proteins: inclusion body quantification. *Proteins: structure, function, and bioinformatics* **72**: 1233.
- Sangram Bagh, Mostafizur Mazumder, Tharsan Velauthapillai, Vandit Sardana, Guang Qiang Dong, Ashok B. Movva, Len H. Lim, and David R. McMillen (2008). Plasmid-borne prokaryotic gene expression: sources of variability and quantitative system characterization. *Physical Review E* **77**: 021919.
- Marco lafolla, Guang Qiang Dong, and David R. McMillen (2008). Increasing the accuracy of bacterial transcription simulations: when to exclude the genome without loss of accuracy. *BMC Bioinformatics* **9**: 373.
- Guang Qiang Dong and David R. McMillen (2008). Effects of protein maturation on the noise in gene expression. *Physical Review E* **77**: 021908
- Guang Qiang Dong, Luke Jakobowski, Marco lafolla, and David R. McMillen (2007). Simplification of stochastic chemical reaction models with fast and slow dynamics. *Journal of Biological Physics* **32**: 67.