MODELING AND ANALYSIS OF ARSR GENETIC CIRCUITS

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Bioreporters are genetically engineered cells that are able to respond to a specific compound with an easily measurable signal. Because cells are cheap to produce and can be integrated in microfluidic devices, bioreporter assays can potentially reduce the cost and facilitate the logistics for the measurement of toxic compounds. Several bioreporters based on the Escherichia coli ArsR system have been previously developed for the detection of arsenic, including strains with tunable response. However, their performances were not optimized for the arsenic concentration limit recommended by the World Health Organization in drinking water (10 µg arsenite L⁻¹). To better understand the key mechanisms of the bioreporters, we developed a comprehensive mathematical model that describes the building blocks of the different circuits (DNA, mRNA, proteins, complexes) and their detailed interactions (binding, synthesis, degradation, maturation) ultimately leading to the fluorescent response. The model parameters appear in two circuit topologies (feedback and uncoupled) and were estimated by scatter search to reproduce the experimental fluorescence measured at different arsenic concentrations. The parameter estimation was further constrained by available ArsR biochemical data. The resulting model is in agreement with feedback and uncoupled circuit configurations, different ArsR alleles and uncoupled promoter activities. Using sensitivity analysis, the model predicted a circuit variant with a steeper response curve at low arsenic concentrations. The strain was experimentally tested and may provide a useful arsenic bioreporter in the field. Stochastic simulations were performed in order to investigate the intrinsic noise of the model. The variability of transcription highlights the influence of circuit topologies, whereas the variability of the fluorescent signal depends on ArsR alleles.