Modeling for Dr. Coli: a synthetic biology approach to intelligent bacterial drug delivery

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Dr. Coli is the 2008 iGEM project of the K.U.Leuven team: an *E. coli* bacterium that produces a drug when and where it is needed in the human body. It does this in an intelligent way, such that the drug production meets the individual patient's needs. And when the patient is cured, Dr. Coli eliminates itself from the body. To achieve this, a molecular timer registers the time since the last disease signal sensed. Then after a certain time, Dr. Coli self-destructs. However, when the disease flares up again – above a certain noise level - the timer is reset and new drug is produced. Finally, the timer will not start counting during the production of Dr. Coli, thanks to its disease-memory.

We designed a proof of concept of Dr. Coli by using standard biological parts (BioBricks). For the input and output of the system, i.e. sensing the disease signal and producing the appropriate amount of drug, we used a dummy system consisting of an anhydrotetracylin responsive regulator and a fluorescent protein, respectively. To obtain self-destruction after a certain healthy period, we placed an inverter, a signal molecule-based molecular timer and a cell death mechanism in cascade. When no input signal is present, the inverter initiates the molecular timer, eventually leading to cell death. Upon renewed presence of the disease signal, the molecular timer is reset. A filter, finally, ensures that the timer is not reset when only "noisy" disease signals are sensed. The memory device, which enables the production of Dr. Coli without it self-destructing, is a stable one-time switch that is activated by the first input signal.

We show here that complex synthetic systems, made up of standard BioBricks, can be successfully designed using *in silico* modelling. Simulations run from an ODE model were used to efficiently assign BioBricks to the Dr. Coli subsystems (e.g. timer and filter) and their interfaces such that the system properties met the desired specifications for intelligent bacterial drug delivery. *In silico* modelling indeed proved essential to captivate and handle the complexity of the genetic network constituting Dr. Coli.

More details on the Dr. Coli project and a full listing of team members can be found at http://2008.igem.org/Team:KULeuven.