

345g Model-Driven Engineering of Regulatable Gene Networks

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Our work focuses on engineering of tightly regulated gene networks for gene therapy applications. Our efforts are resulting in fine-tuned systems in which gene expression can be induced and then repressed at will. Efficiently and reliably turning on and off genes in gene therapies is crucial, for example, in cases where constitutive expression may lead to cytotoxic effects. Because of the large number of participating species in gene transcription systems and the complexity of their interactions, quantitative modeling and engineering offers the best hope for thoroughly investigating dynamic gene expression in a way fit for analysis and design. We will describe innovative computational biology methods for guiding rational engineering of regulatable gene networks. We will specifically describe the investigation of the dynamic behavior of four novel gene networks based on the tetracycline-regulated system and the development of network design principles at the molecular level. The proposed gene network designs are detailed at the molecular level and are attainable with protein and genetic engineering techniques. Typically, proposed designs for gene networks remain unarticulated, lacking adequate detail to be applied experimentally. Armed with supercomputers all the molecular events involved in gene transcription can be accurately modeled. Eventually, the proposed model-driven transcription switches will enable regulation of therapeutic transgene expression, considered a safe and efficient tool in gene therapy.