A Computational Model of CRISPR/dCas9 Genetic Circuits: Towards Programmable Gene Therapy

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Safe, effective, and reliable gene therapy has been heralded as the future of medicine in the 21st century. Technologies for editing and regulating genes based on the CRISPR/Cas9 system have recently emerged as new tools for programmable gene therapy. In particular, deactivated Cas9 (dCas9) fused to either effector domains (KRAB, VP64, etc.) has been developed as a technology for targeted gene activation and repression in vitro. In order to tailor this technology to a variety of clinical settings, mathematical models will be needed to guide the choice of custom design parameters. Here, I present a computational model for the dynamics of dCas9 genetic circuits integrated into mammalian cells by modeling processes such as transcription/translation of guide RNA (gRNA) and mRNA, translocation of complex across the nuclear membrane, binding of gRNA to dCas9, etc. I explore the effects of varying genetic circuit topologies, variable chemical and photo-activated control, degradation rates, and translocation rates on the ability of dCas9 genetic circuits to regulate multiple genes. In the future, my results could guide synthetic biologists and clinicians alike to develop programmable gene therapies for a variety of genetic disorders.

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