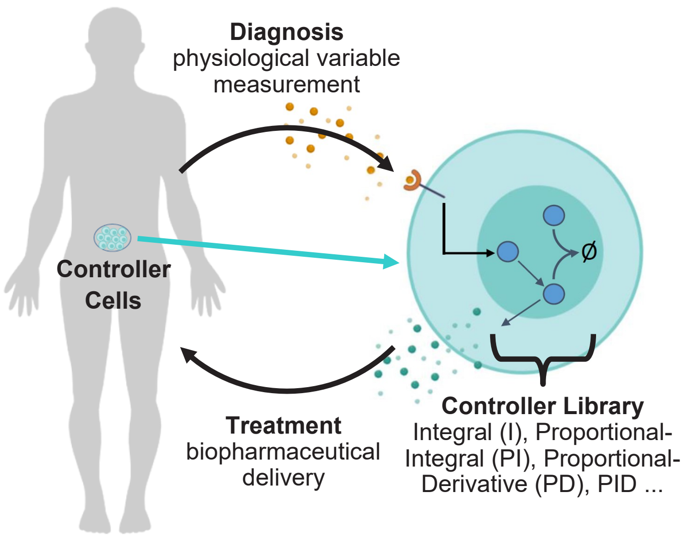
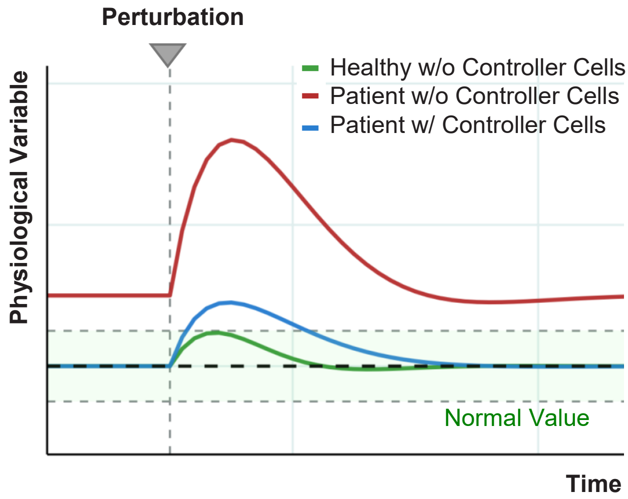
ETH zürich

Licensing Opportunity

Robust and precise genetic feedback control systems for cell therapy





Application

Proportional-integral-derivative (PID) control systems are the most widely-used devices for regulating all types of processes in industry. Synthetic, genetic circuits that realize PID control systems can robustly steer the behaviour of gene networks and cells, making them powerful tools for cell therapy. Applications include monoclonal antibody production, cancer immunotherapy, chronic inflammatory diseases, metabolic disorder diseases and regenerative medicine.

Features & Benefits

- Autonomous control of therapeutic dose
- Best therapeutic efficacy
- Reduction of side effects
- Robust to interpatient variability (age, sex, disease status)

Publications

- “Genetically Engineered Integral Feedback Controllers for Robust Perfect Adaptation in Mammalian Cells” (bioRxiv)
- “A class of simple biomolecular antithetic proportional-integral-derivative controllers” (bioRxiv)

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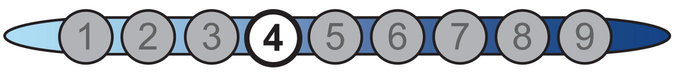
Technology Readiness Level



Background

Biological organisms profit from natural feedback loops that steer biological functions towards conditions optimal for survival (e.g. body temperature, oxygen levels). This process of self-regulation is known as homeostasis. Synthetic biology offers the ability to realize artificial feedback loops that can adjust therapeutic protein dosages or step in for dysfunctional natural feedback loops. Currently available artificial genetic circuits lack robustness towards fluctuations of their environment, especially when very tight regulations are required.

Invention

For controls systems to be precise and robust, feedback strategies are required that incorporate dynamic integral feedback actions. A proof-of-concept has been established in mammalian cells for a robust PI control system and an extension to a hierarchy of PID controller networks is proposed. In an example application the controllers are employed to limit the inflammation response in CAR-T cell therapy to avoid adverse outcomes such as cytokine release syndrome. A control system has genetically modified cells that express the respective control circuits, all of which contain an antithetic motif realized by biomolecules. For the application, the controller is functionally linked to the production of the target cytokine that needs to be controlled or the production of biopharmaceuticals specifically inhibiting the target cytokine. More precisely, the control system acts on the target cytokine concentration depending on the mathematical integral of the difference between the measured concentration and a desired set-point. This results in perfect adaptation of the cytokine concentration, that is, the difference between output level and set-point is driven to zero over time. Besides integral control responsible for perfect adaptation, this invention includes a library of advanced controller designs, which allow the control system to provide better transient dynamics and to handle noisy single-cell dynamics.