Internet of Cells (IoC) for *In Silico* Feedback Control of Protein Levels in Multiple Cells

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Project Description

Proteins are "worker" molecules necessary for nearly all processes, including metabolism, growth, cell division, adaptation, communication, etc., within a cell and between cells. Since protein activity is generally governed by concentration, cells control protein concentration to modulate intracellular and intercellular processes. Therefore, the capability of artificially controlling protein levels in living cells can be immensely useful for unraveling the mechanism of complex intracellular and intercellular processes. Recently, it has been demonstrated that protein levels can be controlled using light, which is called optogenetics (**Figure 1A**) [1]. Real-time *in silico* feedback control of protein levels using optogenetics in the presence of biological noise has also been reported (**Figure 1B**) [2, 3]. However, these demonstrations are not designed for studying complex multicellular interactions, which depend not only on interactions

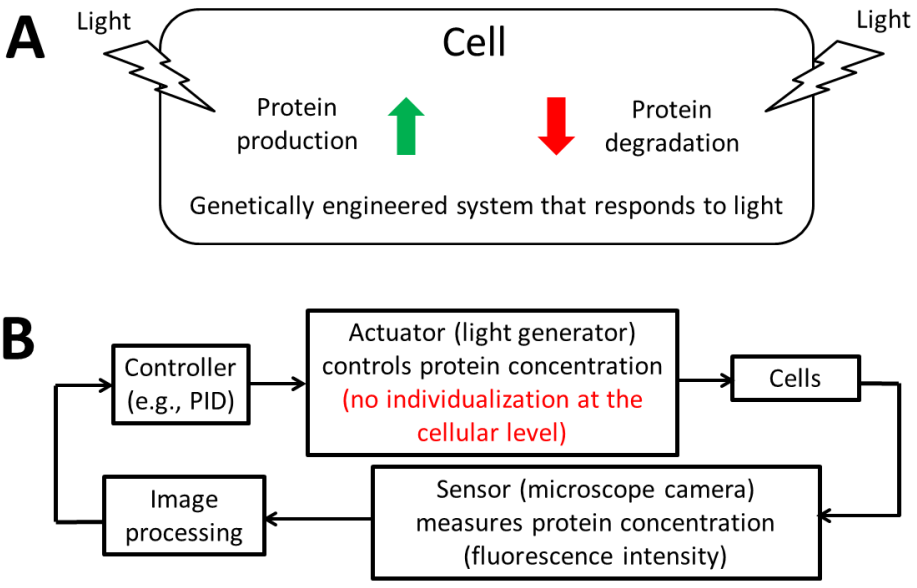

Figure 1. (A) Optogenetics. (B) Real-time *in silico* feedback control of proteins levels using optogenetics.

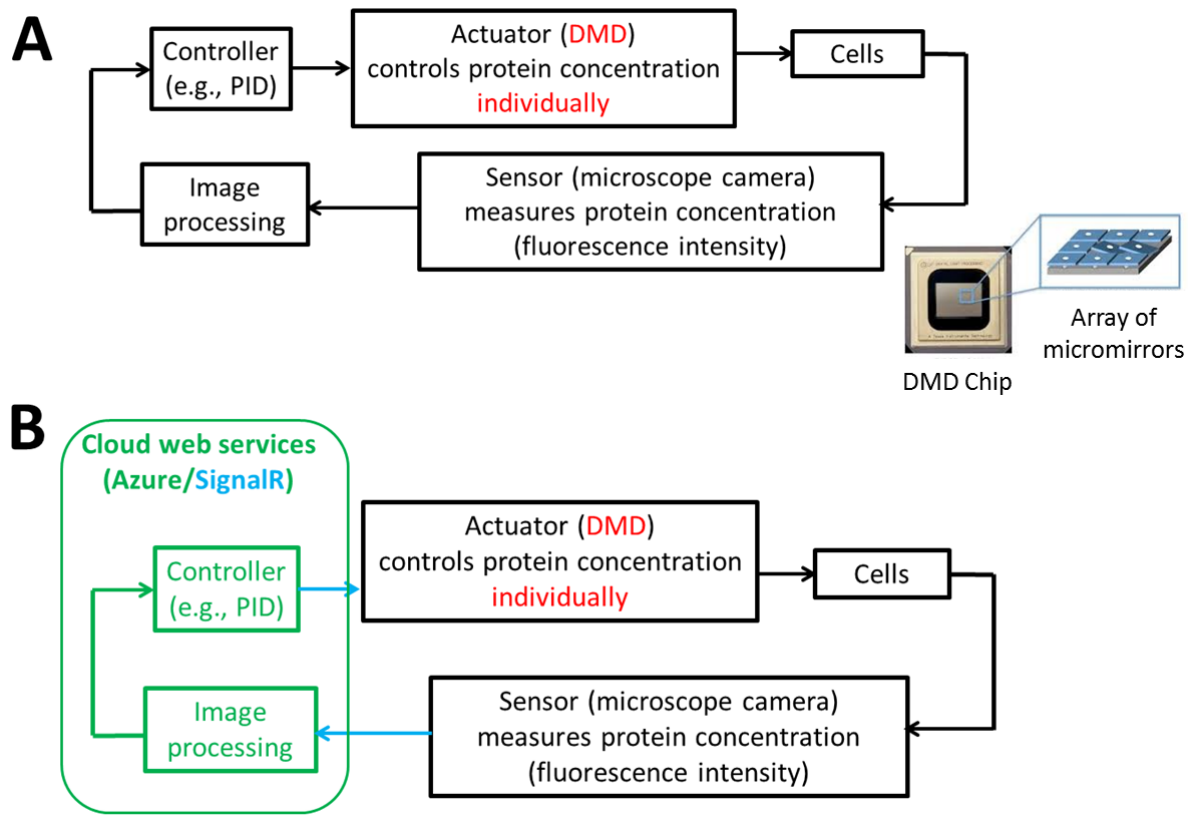

Figure 2. (A) *In silico* feedback control of protein levels in multicellular systems using optogenetics and Digital Micromirror Device (DMD). (B) Internet of Cells (IoC).

between cells but also on individualized cell dynamics. Such capability will be critical in addressing protein function at the tissue level, and therefore has immediate translational value. The objective of this project is to develop *in silico* feedback control of protein levels in multicellular populations using optogenetics and Digital Micromirror Device (DMD) [4], an array of micromirrors that can be used for giving tailored color and light intensity to individual cells (**Figure 2A**). This experimental platform can be useful for studying complex multicellular behaviors, such as collective decision making and cooperative control, which will have broad impact not only on systems and synthetic biology but also on related multi-agent research areas such as adaptive sensor networks and swarm robotics. Furthermore, image processing and DMD control algorithms will be available on a cloud platform (Azure) as SignalR-based web services [5-8], enabling "Internet of Cells (IoC)" (**Figure 2B**). This is a community-based, open-source platform where scientists and engineers can readily use available algorithms across the internet in real time and also share their own algorithms with the community. The PI selected well-tested technologies, mainly SignalR and Azure, to focus on productive development of a new biomedical Internet of Things (IoT) application and not on internet or cloud computing issues, such as robustness, resilience, stability, privacy, security, etc., although they are important in their own right.

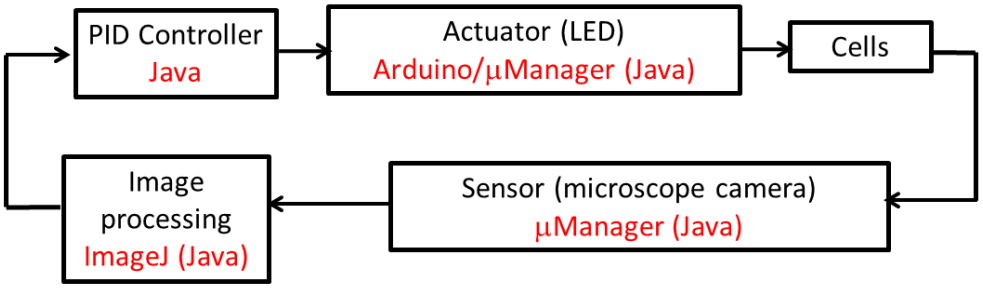

Figure 3. An integrated Java application for PID control of protein levels within a single cell.

Preliminary Data

We were able to induce protein degradation in yeast cells using blue LED light. The reason we focus on degradation regulation mechanism first is that modulating protein degradation can be superior to protein production regulation in terms of robustness and agility, as suggested by the PI previously [9]. Pros and cons of degradation only, production only, and combined regulation mechanisms will be examined in this project. We are currently working on achieving desired protein levels over time within a single cell using the PID feedback control algorithm widely used in engineering (**Figure 3**). No DMD and cloud computing are involved at this stage. It is notable that a single integrated Java application, which makes use of ImageJ and µManager, manages all the processes including microscope/camera operation, image processing, and PID control of LED using an Arduino (shown in red in **Figure 3**). µManager is an open-source, cross-platform desktop application whose Java API interface can be used to control a wide variety of motorized microscopes, scientific cameras, stages, illuminators, and other microscope accessories [10, 11]. Combined with ImageJ [12], a public domain, Java-based image processing program developed at NIH, µManager provides a mature platform for biological microscope imaging. Furthermore, µManager supports DMD, which is one of the critical components of this project [13]. Eventually, the integrated Java application will communicate with SignalR-based cloud web services, enabling IoC shown in **Figure 2B** [5-8]. Protein level control is a relatively slow process, which takes minutes and hours, so network issues such as communication latency can be safely ignored.

Available resources:

1. Feedback control and DMD: PI Prof. Shin has expertise in applying control and estimation theory to systems biology and expertise in digital microfluidics/bioMEMS (MicroElectroMechanical System) including DMD.
2. Optogenetics: Co-PI Prof. Cho has expertise in optogenetics and synthetic biology.
3. Cloud environment: In May 2015, PI Prof. Shin, Prof. Rajasekaran (UCONN Computer Science and Engineering), and Prof. Ramprasad (UCONN Material Science and Engineering) jointly received $1.4 M for building a cloud-enabled HPC infrastructure on campus, which will be used for building a private Azure cloud platform described in this project. The PI also received Microsoft Azure Research Award twice (2014 and 2015) and has required experience of using Azure cloud resources and services for the project.

4. Software development environment: NetBeans (Java), Visual Studio Community 2015 (C++/C#), and IntelliJ IDEA (Javascript), and GitHub are freely available and will be used for this project.

Major required resources:

1. 2 graduate student RA support for 3 years
2. Andor Mosaic 3 [13] or comparable DMD package for microscopic imaging

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