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Engineering at the Cellular Scale:
Understanding and manipulating information processing networks

Aiman Alam-Nazki

Systems biology is an interdisciplinary field of research that seeks to understand the complexity and functioning of biological systems and processes in a systematic manner. The intricacies of biological systems can be studied at different scales/levels (population, organism, tissue or cellular level). This article will primarily focus on understanding biological processes at the cellular level- particularly the intracellular level, through quantitative approaches. Quantitative approaches are not new and have been used for quite some time in the study of biology. However, the nature of quantitative research has evolved to become more integrated with inputs and approaches from the natural sciences, engineering, computer science and mathematics. Furthermore, the discipline of "Synthetic Biology" has emerged in the recent decade where the understanding of biological function and processes is being applied to engineering and designing biological systems. With potential applications ranging from personalized therapeutics and healthcare to bioenergy and micro-level bio-factories to DNA computing, both Systems and Synthetic Biology have the potential to push the boundaries of science and technology, further and deeper, at scales that have largely been out of reach till now.

Engineering plays multiple important roles in Systems and Synthetic biology. The foundation of training of all chemical engineers, for example reaction engineering, transport phenomena, systems engineering, control, naturally lends itself to understanding or manipulating biological processes, especially complex chemical networks in cellular processes, though many new challenges arise as well. A key role of biochemical (and gene regulatory) networks in cells is *decision-making* in response to signals received from the environment. Examples of such decisions are growth, division, differentiation and movement in a particular direction. Thus these networks act as the core controlling hubs of cells and the manner in which signals are processed through these networks, i.e. *information processing*, is a topic of central importance in systems biology. On the face of it, information processing simply involves molecules interacting with one another in networks through chains of reactions; however a closer look reveals many other important underlying features: the complexity of these networks is not only a function of the number of species in the network but more importantly due to non-linearity, widespread feedback control, stochasticity, spatial effects (not to forget the subtle organization of the networks), driving the information processing.

An example of a decision is chemotaxis or cell migration in response to gradients of chemical cues. Cell movement is observed in important biological phenomena in a wide range of systems from bacteria to eukaryotes. Some examples are the development of the embryo, nervous system development, migration of tumors and action of the immune system (Figure 1). If the underlying networks malfunction, it may result in congenital defects and other diseases. Understanding the functioning of the networks underlying chemotaxis has wide-ranging applications from nerve injury and regeneration to development of therapies in cancer and other diseases to re-engineering organisms to seek and degrade toxins in the environment.

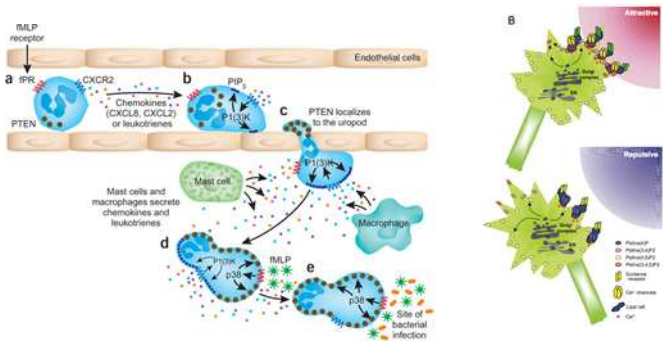

Figure 1 (Left) Chemotaxis in white blood cells[1]. (Right) Directional migration in neurons in response to different chemical signals[2]

Chemotaxis is an example of a vital cellular process. While it is easy (and fascinating) to visualize, understanding how molecular networks inside cells combine to robustly orchestrate this process is challenging. Indeed, it involves molecular networks with a moderate number of components (relative to other cellular processes), which is nevertheless complex because of the strong nonlinearity (vital to this process), multiple feedback regulation, spatially distributed components and close interaction with mechanical elements in the cell.

From an engineering point of view the process can be loosely broken down into three conceptual stages- 1. Sensing- where the chemical cues in the cellular environment are received as signals by the cell and converted into other internal signals to guide cell motion, 2.

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Polarization- where downstream chemical networks in the cell interact and strongly spatially re-distribute themselves to form a front and back; which leads to the last stage 3. Movement- the redistribution leads to movement in a particular direction, propelled by the polymerization of F-actin. These three processes (Figure 2) are governed by distinct chemical networks, which collectively orchestrate the decision to move towards or away from the cues in the environment.

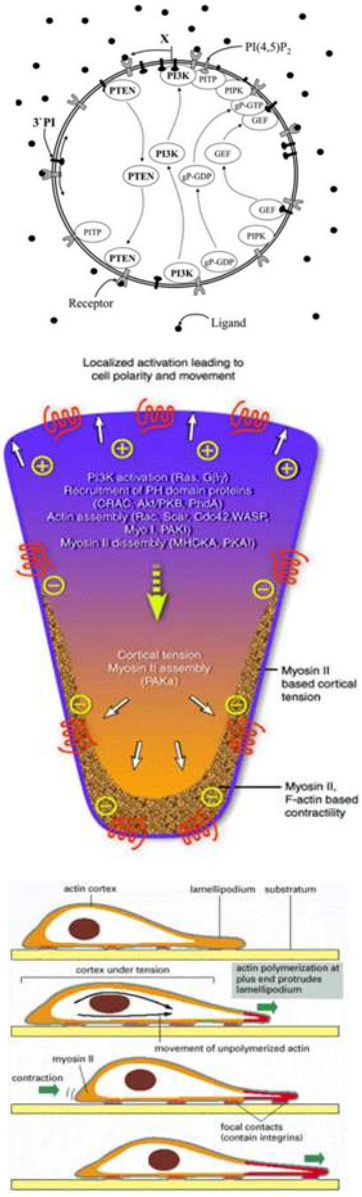

Figure 2 Three stages of movement

Several approaches are used to understand these stages and their interaction in moving cells. I present a brief example of some of our work in this area to highlight how different complementary approaches can be brought to bear in this respect. We use a combination of mechanistic modelling and systems engineering approaches to investigate organization and signal flow through chemotactic cellular networks and control mechanisms therein. In the initial part of our study, we focused on the decision where cells move away from a chemical cue or chemorepulsion and we used a mechanistic modelling approach here. *D. discoideum* is an experimentally well-characterized organism with a number of experiments pertaining to chemotaxis. Keizer-Gunnink et al.[6] hypothesized a biochemical network (Figure 3) underlying chemorepulsion in this organism based on a number of their experiments.

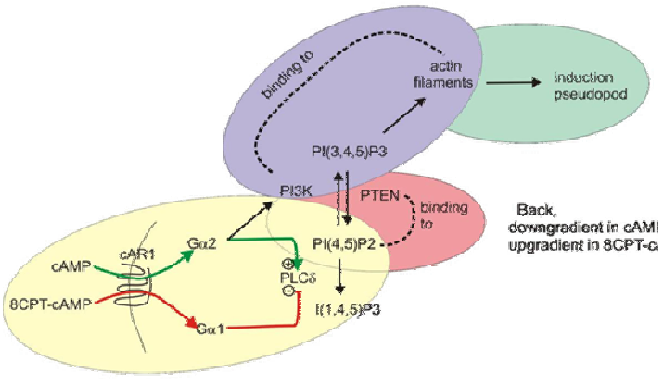

Figure 3 Biochemical network hypothesized by Keizer-Gunnink et al. underlying chemorepulsion in *D. discoideum*[6]

Using a systems based approach, we created a PDE modeling framework, incorporating the kinetic interactions and transport in which we analyzed this network and its interactions. Ours was the first mathematical modeling investigation of chemorepulsion. We took the network apart piece by piece and studied the different interactions within, which included multiple feedback and feedforward loops, as well as the role of diffusion of individual species. The goal was to understand how this network is wired to give the desired repulsive response and if the interactions posed in the biological network are enough to realize this response or if additional interactions are needed. A number of other potential interactions were also studied. We found that either additional feedforward regulation of certain key enzymes is needed in addition to the postulated feedback or certain key enzymes must be acting at saturation in combination with one specific feedback interaction to give the desired repulsive behavior. Since conducting this study, experimental groups have been finding different processes in which chemorepulsion is implicated and plays a key role[7]. For example, Amatschek et al.[8] have proposed that chemorepulsion may be one of the mechanisms utilized by tumor cells in melanoma to migrate to different parts of the body. Understanding chemorepulsion is also being applied towards developing immunotherapies.

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Our initial study focused on chemorepulsion in a particular biological organism. A survey of the signaling landscape shows that chemotaxis is seen in a range of different systems. We wanted to understand how networks are wired and organized in different systems to make these migratory decisions. During our investigation of chemorepulsion, we knew obstacles would present themselves in the form complex, non-linear networks that involve multiple feedback interactions and that are spatially distributed. Details of each network vary between different biological systems (even with similar components) and information about kinetic and transport related parameters is often missing. With developing experimental techniques some details keep getting refined. We therefore sought to complement our mechanistic modelling with a new systems-design approach which addressed some basic aspects of the process without getting bogged down in details which take a long time to be experimentally elucidated. We started by noting that multiple cell types systems have been experimentally observed to show *both* chemorepulsion and chemoattraction to different and sometimes to the *same* signal. We therefore decided to investigate, in depth, the organization of the networks which allowed for this, consistent with other signaling characteristics exhibited by these cell types.

We addressed these challenges by creating a systems framework to study some key design features of these networks[9]. This approach involved isolating building blocks that are representative signaling network characteristics seen in concrete cell types. These building blocks represent key qualitative behaviors (for example local sensing, adaptation and spontaneous polarization) observed in different cells. We analyzed the consequences of having different types of network wiring design features that are hypothesized in the literature to lead to directional migration- the so-called polarity switch and competing pathways, upstream of each of the building blocks (Figure 4), and analyzed multiple other design scenarios as well.

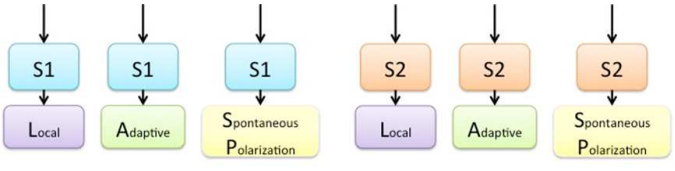

Figure 4 S1 and S2 are the design features upstream of the individual building blocks that encompass essential qualitative features observed in real systems[9]

The articulation of the above questions and the formulation of such a framework allowed us to analyze design principles and features, which might allow cells to exhibit attractive and repulsive response to either the same or different signals. It provides new insights into the design, constraints and tradeoffs in networks which control both chemorepulsion and chemoattraction. In fact, it also provides insights into hidden constraints which may limit the extent to which signaling can be manipulated. Both the approaches we have used complement one another: it allows us to analyze and tease out specific mechanistic details in individual systems, and also understand broader aspects of the wiring and organization, which are relevant to multiple systems.

This dual approach acts as a platform to understand bidirectional cell movement in a broad range of cell types and forms the basis of starting to examine how the migratory behaviour may be exploited or reversed. Finally, using such complementary engineering-based approaches is useful in other biological and biomedical related applications to effectively understand and control cellular behaviour.

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