Using Biological Systems as an Analog-to-Digital Converter

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Abstract

Biological systems can create complex structures from very simple systems. To do this, there must be a method to differentiate different regions where identical systems create different structures, such as the abdomen and the head of a fruit fly. Because the differentiation methods in real biological systems are not fully understood, we decided to create a differentiation method based on an analog-to-digital converter using bacterial cells in a concentration gradient. By creating a biological circuit in the bacteria that act as threshold detectors, we can determine the concentration of a chemical at a given distance away from the point source. Then using another biological circuit, we can produce a new concentration gradient that has twice the frequency. If 1 is represented by a concentration of the chemical within the threshold, and a 0 is represented by a concentration outside the threshold, then we can represent any two digit binary number. Thus, we can differentiate separate regions at certain distances away from a point source.

1.0 Introduction

Biological systems have the immense capability to generate complex structures from very simple systems. With simple rules and few inputs, a biological system can grow from a single cell to a multicellular organism in a relatively short amount of time. The sophisticated underlying framework of these systems is extremely powerful, but unfortunately is also beyond anything we can construct with our current technology. However, instead of constructing a complex system, we can tailor the biological system to fit our needs. To show that these systems can be useful, we will build a biological analog to digital converter.

There are many applications for this technology. The scale of technology has been steadily decreasing, and conventional methods of fabrication and production are facing obstacles that are insurmountable. Physical manipulation of substrates will no longer be able to satisfy our need for nanoscale accuracy. Biological systems, however, have been accurately synthesizing nanoscale machines for millions of years. By studying the genetic regulatory pathways and the interactions between proteins, we hope to gain an understanding from an engineering point of view that will allow us to progress towards fully exploiting the potential of biological systems in an engineering process.

2.0 Background

The Drosophila (*Drosophila melanogaster* or the Fruit Fly) is one of the most widely studied systems in terms of its development. The larvae have been studied extensively in an attempt to understand the complex cellular differentiation processes that give rise to the various body parts and organs. Even though we have only very basic understanding of these processes, some of the fundamental ideas have been elucidated from the numerous studies performed.

Segmentation, the development of segments in the body of the larvae, is perhaps the most significant process because the underlying structure of the fly is defined at this stage. However, the input for this complicated process is not complicated at all. The initial input consists of only two inputs: two chemical gradients that have sources located at opposite ends of the larvae [1]. That is, one gradient comes from the anterior end, and the other comes from the posterior end. Transcription factors that are already present in the larvae respond to the varying concentrations of these two signaling chemicals and begin the differentiation process by initiating the transcription of the first level control

genes. These gap genes then in turn activate or repress the expression of what is known as the pair-rule genes.

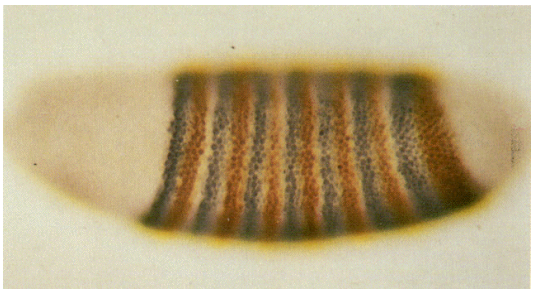

Figure 1: A photograph of the staining of two gene products in a Drosophila larva. The distinct pattern of the two different proteins can be easily seen. (Source: P. A. Lawrence. *The Making of a Fly: The Genetics of Animal Design.* Blackwell Science Inc, Boston, MA: 1992)

The pair-rule genes have a very interesting expression pattern. These pair-rule genes are not expressed in a conventional gradient pattern, but rather in an alternating pattern with distinct borders (see Fig. 1). We decided to study this pattern of expression as the basis for our project in designing a biological analog-to-digital converter.

However, when we investigated this system further we realized that this is not an ideal system for us to manipulate. For each of the stripes present in the larvae, there is a unique locus that controls the expression at that particular stripe. That is, to generate the expression pattern in figure 1, there are fourteen regions in total that are involved in the control of this particular pattern. This is simply too complicated and impractical for us to attempt to manipulate. The problem with scaling is one of the many challenges that this system cannot overcome. With each location requiring a singular control region, as the desired number of stripes increase, the number of controlling regions grows linearly. We decided to engineer a simpler solution for our construction of the biological analog-to-digital converter.

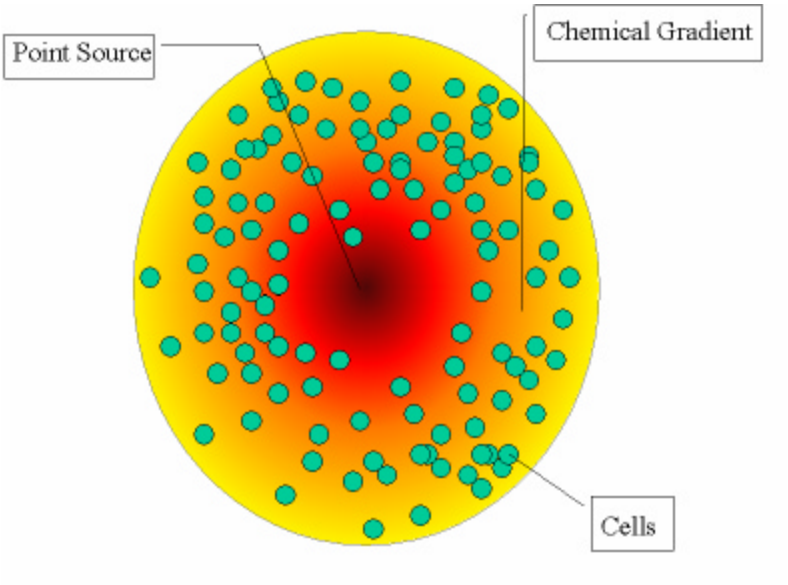

Figure 2: E. coli Cells in a point source chemical gradient

3.0 Bacterial Cells in a Concentration Gradient

3.1 The Setup

For this biological system, *Escherichia coli* bacteria cells on a set plane are introduced to a point-source chemical gradient (see Fig. 2). The chemical causes the cells to produce a protein when the concentration is above a certain threshold. The goal is to produce a sigmoidal curve such that two states, specified 0 and 1, are distinguishable [2].

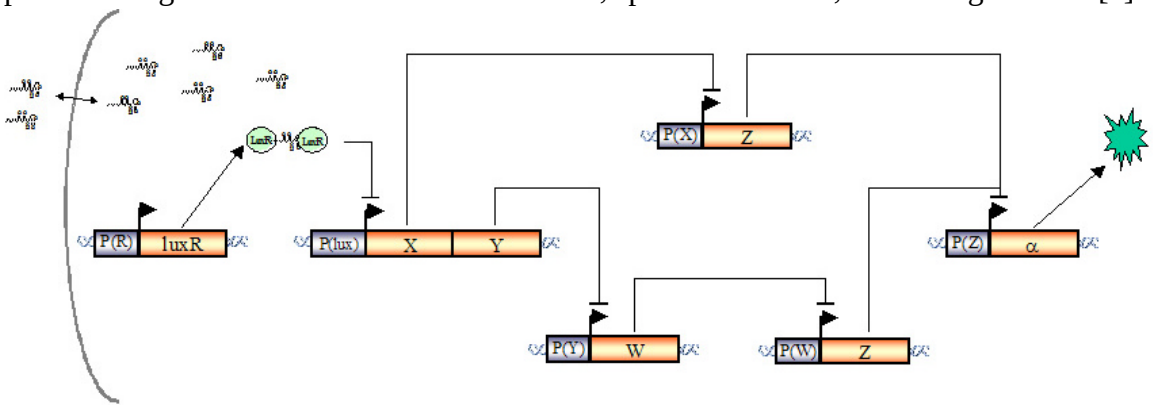

Figure 3: Genetic Circuit for Chemical Concentration Band Detector
(Source: R. Weiss. Cell-Cell Communication. In *Computing Beyond Silicon Conference*, Pasadena, CA, July 2002)

Each E. coli cell is engineered to be a chemical band detector based on Ron Weiss's work. In general, the genetic circuit detects the concentration of a chemical within a specified range and produces a new protein. The mechanism for the circuit is as follows: Chemical 1 diffuses from the point source into the cells and binds with a cytoplasmic protein, allowing the protein to dimerize (see Fig. 3) [3]. The dimer binds to the DNA and activates the P(R) promoter, which produces protein X and protein Y. Protein X will then bind to P(X) and repress the production of protein Z_1. Protein Y will bind to P(Y) and repress the production of protein W, a protein which represses the production of Z_2 at the P(W) site. The production of Z_1 sets the lower threshold and Z_2 sets the higher threshold. When the concentration of chemical 1 is within the threshold region, protein α is produced. The concentration of protein α will produce a sigmoidal curve.

From the concentration of protein α and chemical 1, another genetic circuit (gradient-creation circuit) in the E. coli cell creates a new concentration gradient of chemical 2 with twice the frequency of the sigmoidal curve. Ideally, the concentration of chemical 2 equals the concentration of Chemical 1 subtracted by the concentration of protein α ([C2] = [C1] – [Pα]). To achieve this, protein α must inactivate chemical 1 at a linear rate. Chemical 1 then dimerizes and binds to P(S), which produces chemical 2.

From chemical 2, a similar genetic circuit based on the chemical band detector will produce protein β. Similar to the interaction between protein α and chemical 1, Protein β inactivates chemical 2 to create the next concentration gradient with double the frequency of the expression of β. As long these main circuit elements are created for each sigmoidal curve, the bacterial cells in a concentration gradient can produce more sigmoidal curves with double the frequency of the previous level.

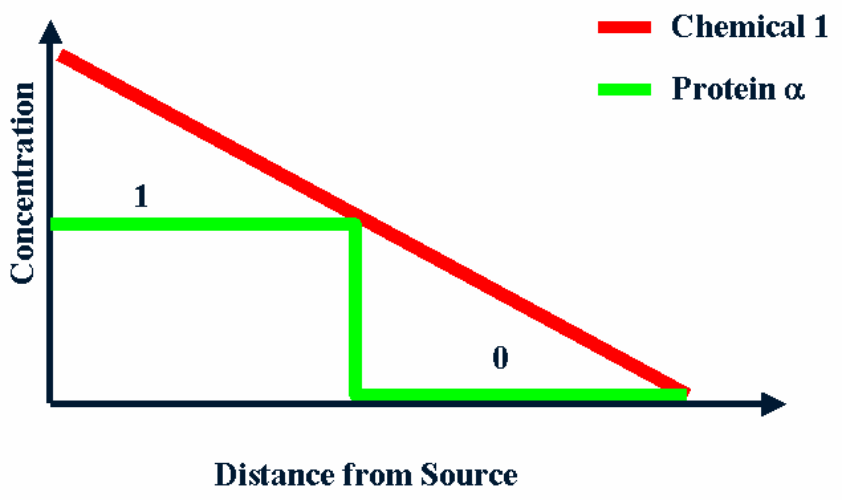

Figure 4: Approximation of a sigmoidal curve (green curve) from an approximated chemical gradient (red curve)

3.2 Creating the Digital Abstraction from Analog Signals

From the basic genetic circuits described above, a bacterial cell can be programmed to produce the sigmoidal curves necessary in our A-D converter based on a simple threshold detector. The importance of the sigmoidal curve is that it provides a sharp transition between two states (see Fig. 4). Because of the sharp transition, the two states, 0 and 1, can be easily distinguished (see Fig. 4). The presence of two distinct states allows for a straightforward digital abstraction from the sigmoidal curves.

Starting with an initial concentration gradient of chemical 1 from the point source, the bacterical cells create a sigmoidal concentration curve of protein a using the band detection circuit (see Fig. 4) (refer section 3.1). A gradient-creation circuit then utilizes both chemical 1 and protein a to produce a new concentration gradient of chemical 2 (see Fig. 5). Using a second band detection circuit that will detect the presence of chemical 2, the bacterial cells create a sigmoidal concentration curve of protein ß which has double the frequency of protein a's curve (see Fig. 6).

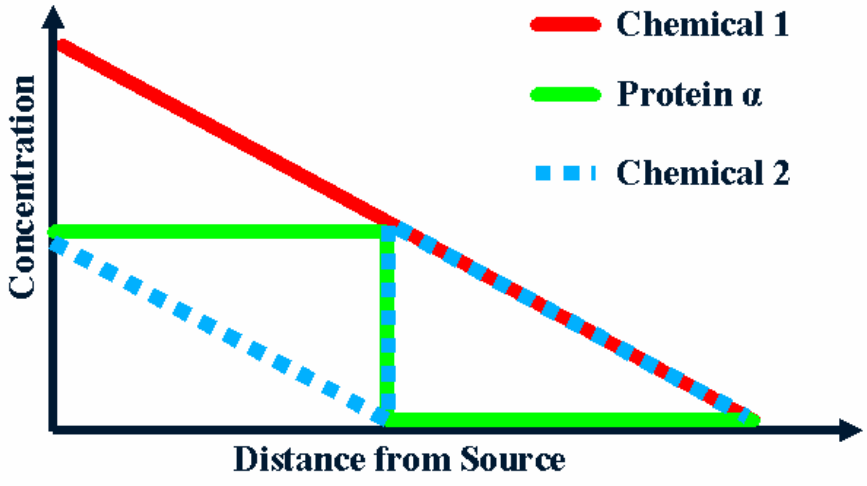

Figure 5: Creating a concentration gradient of chemical 2 from chemical 1 and protein a. Chemical 2 = Chemical 1 - Protein a

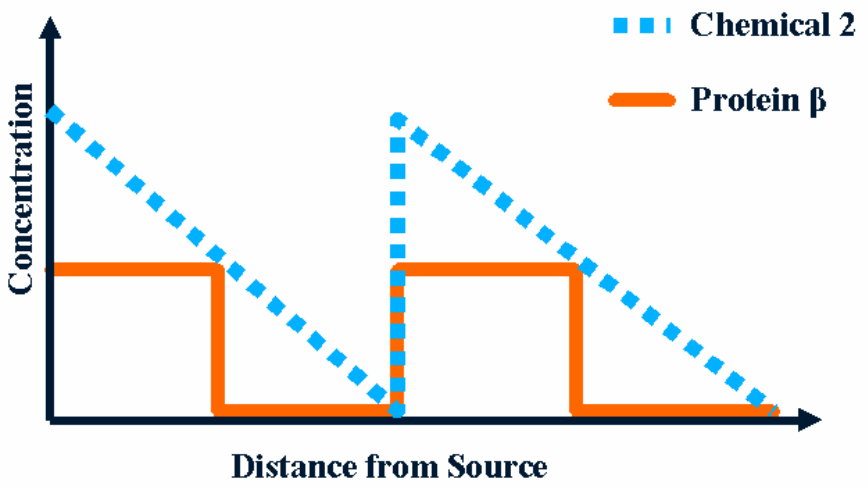

Figure 6: Creating a sigmoidal curve of protein ß from chemical 2's concentration gradient

Each sigmoidal curve represents a specific digit in a binary number. Curves with a lower frequency represent more significant digits, and curves with a higher frequency represent less significant digits (see Fig. 7). Thus three sigmoidal curves will represent all the 3-digit binary numbers.

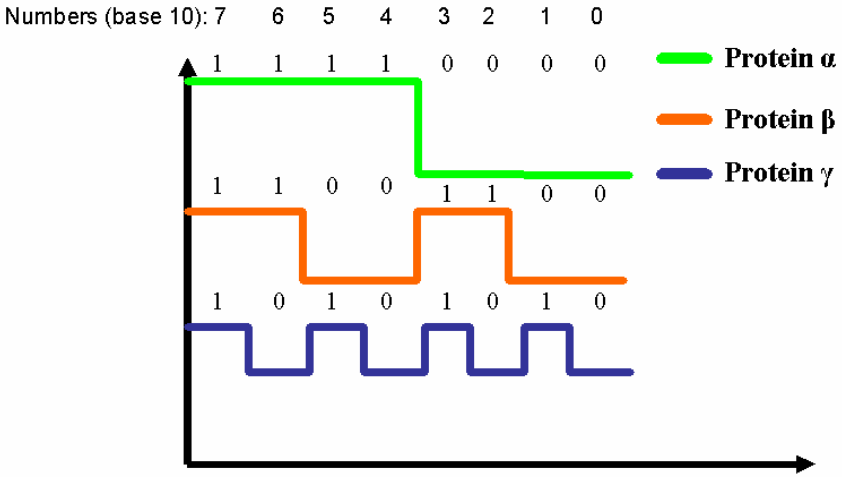

Figure 7: Representation of all three digit binary numbers using the sigmoidal curves

4.0 Work In Progress

With the basic layout for the analog-to-digital converter explained above, it should be possible to build an arbitrarily large converter that can represent any binary number with the necessary number of digits. To do this, there must be a list of all the chemicals and proteins that can be detected by the band detection and the gradient-creation circuits. The chemicals cannot be overly reactive with each other, or else there will be lots of noise in the system, compromising the clarity of the binary representation. Similarly, the proteins cannot counteract each other. The size of the biological A-D converter will thus be limited by this restriction.

The thresholds for the chemical band detection must be determined. If the thresholds are set correctly, we can then have sigmoidal curves that double in frequency between each level. The doubling of frequency is crucial to representing all the possible

binary numbers with a given number of digits in this system. Otherwise, if the thresholds are set incorrectly, the sigmoidal curves will oscillate at unexpected frequencies, causing the analog-to-digital converter to fail to be useful because the resulting curves are undeterministic.

5.0 Summary

We have described a basic framework for building an analog-to-digital converter using a point-source chemical gradient and E. coli bacteria. By designing the bacterial cell to act as a chemical band detector and a chemical gradient creator, we can in theory create an arbitrary large digital system from the analog chemical gradients in the system. We will in reality be limited by the amount of interference between chemicals and proteins, but hopefully with further refinement to the circuits, the amount of interference will be reduced.

References

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