GeneVis: Visualization Tools for Genetic Regulatory Network Dynamics

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ABSTRACT

GeneVis provides a visual environment for exploring the dynamics of genetic regulatory networks. At present time, genetic regulation is the focus of intensive research worldwide, and computational aids are being called for to help in the research of factors that are difficult to observe directly. GeneVis provides a particle-based simulation of genetic networks and visualizes the process of this simulation as it occurs. Two dynamic visualization techniques are provided, a visualization of the movement of the regulatory proteins and a visualization of the relative concentrations of these proteins. Several interactive tools relate the dynamic visualizations to the underlying genetic network structure.

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Keywords: biological visualization, visualization, multi-representation, genetic networks, lenses, focus and context

1 INTRODUCTION

Since the mapping of the human genome, research interests in biology have shifted towards the issue of discovering what the genetic code actually does. This includes such questions as: what proteins do genes code for? how does this affect the development and functioning of the organism? how do genes communicate appropriate information to each other? how do genetic networks function? and what are their dynamics?

We consider genetic networks to consist of sets of genes that are regulated by sets of proteins. When genes in the network express they trigger the production of proteins, which in turn can regulate the expression of other genes, thus creating a network of dependence. Gene expression can exist in a relatively steady state of protein production, but the activity levels of genes can also change over time. With techniques such as DNA micro-arrays [10] it is now possible for biologists to measure, in parallel, the activity levels of genes as a function of time. Biologists may use these temporal measurements to infer which genes interact with which ones and what are the patterns of these interactions. However, this is a non-trivial exercise. The data is expensive and difficult to obtain, and can be noisy. Furthermore, even relatively small genetic networks may have complex dynamics due to positive and negative feedback loops. To assist in the process of inference, models of the observed genetic activity are being developed. These models can be used to create simulations and visualizations, helping us form mental constructs of the behaviour of regulatory networks and thus further our understanding them. In order to provide this comprehension, we have created a Simulation and visualization environment called GeneVis. In GeneVis spatial organization of the simulated entities is used and adjusted interactively in order to help illustrate and support the exploration of mental concepts. Moreover, different visualization techniques can assist in understanding different aspects of the same data set.

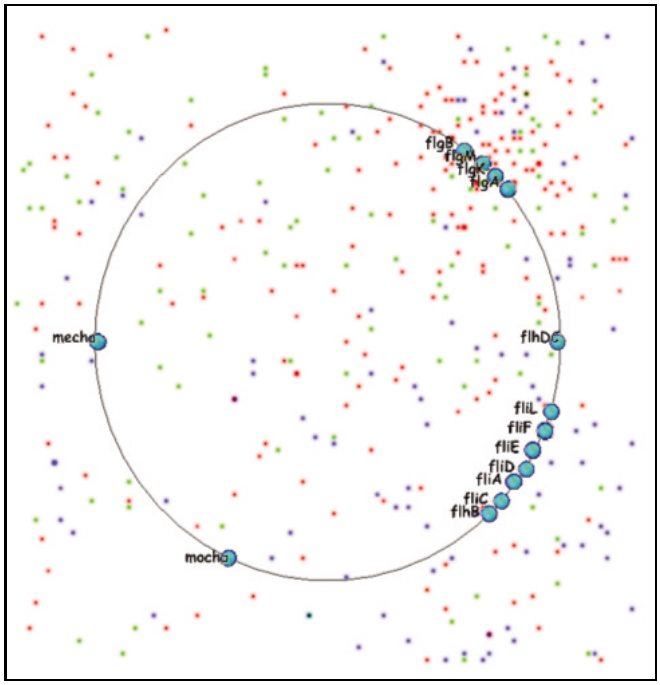

Figure 1: A screenshot of GeneVis: The large circle in the middle of the screen represents the chromosome. Around the circle there are small spheres, which represent genes. The small fuzzy dots throughout the image represent proteins.

GeneVis has been designed for use with prokaryotic organisms [5]. It simulates genetic network behaviour using probabilistic occurrences of gene-protein interactions, and creates visualizations of the genetic network dynamics as they occur during the simulation. In this paper, we focus on the visualization aspects of GeneVis. The visualization environment supports several representational modes, which include: a *protein interaction representation*, a *protein concentration representation*, and a *network structure representation*. The protein interaction representation shows the activities of the individual proteins. The protein concentration representation illustrates the relative spread and concentrations of the different proteins in the simulation. The network structure representation depicts the genetic network dependencies that are present

in the simulation. Figure 1 shows GeneVis in the protein interaction mode.

GeneVis incorporates several interactive viewing tools. These include animated transitions from the protein interaction representation to the protein concentration representation, and from the protein interaction representation to the network structure representation. There are also three types of lenses: *fuzzy lenses*, *base-pair lenses* and the network structure *ring lens*. With a fuzzy lens an alternate representation can be viewed in a selected region. The base-pair lenses allow users to reposition genes for either better viewing or to minimize interference during the simulation. The ring lens provides for detail-in-context viewing of individual levels within the genetic network structure representation.

2 Genetic Network Behaviour

A genetic network consists of a set of genes that are related through a collection of regulatory proteins. Each gene may require an input and may produce an output. A gene's output results in the production of either regulatory or constructive proteins. Regulatory proteins act as inputs for the other genes and affect their expression, while constructive proteins make up the physical structure of the organism.

A gene receives input through the binding of regulatory protein(s) to one or more of its operator sites. The bound regulatory protein then promotes (or inhibits) the gene's transcription and subsequent expression. Each regulatory protein binds to specific operator site(s) based on biochemical laws of interaction between molecules [10]. Thus, only specific proteins are able to bind to particular sites on genes. Variations in binding affinity are based on the DNA sequences of operator sites. The genes and their characteristics (affinity, operator site(s), proteins expressed, etc.) can be used to create a rule set, on which simulations of the genetic network dynamics are based.

Genetic network behaviour is highly probabilistic. The fluctuating numbers and positions of proteins determine the likelihood that a requiring gene will express. The higher the concentration of a protein, the greater the chance that it will come in contact with a gene that requires it. In addition, proteins decay at different rates, which also affects the probabilistic cellular dynamics.

Previous genetic regulation visualization research was focused on the representation of the genetic network structure. This structure has been commonly represented using directed graphs as in GeneGraph [16], WebGen-Net [19], and GeneNet Viewer [8]. There have also been different simulation models created, such as Random Boolean Networks [18], NetWork [17], Circuit Simulation [12], GeneNet Modeller [13], Genetic Network Analyzer [4], StochSim [14], and BioSim [6]. The results from these simulations have been presented as charts, in which the simulated gene activity levels have been plotted as functions of time. While these programs do consider static and dynamic data, their visualizations are not dynamic. They display either a static network structure or a static representation of the simulated dynamics.

3 Visualizing the Simulation

GeneVis uses random protein movement to simulate the probabilistic interactions in genetic networks. By this random movement, proteins disperse throughout the simulation environment. The cell is modelled as a grid that wraps around on all four sides so that proteins can circulate through the environment continuously (see Figure 1). How each protein moves is randomized in the choice of distance and of which of the eight possible directions to take.

In GeneVis the simulation starts in the initial state in which no proteins are present and the genes are operating at their basal activity level. This means that each gene's expression is neither promoted nor inhibited by a bound protein [10]. This basal level activity results in the production of some proteins, which spread throughout the environment and start interacting with the genes, promoting or inhibiting their expression.

3.1 Protein Interaction Representation

In visualizing the interactions between the individual proteins and genes, we:

- use the base-pair positioning [5] to depict the actual locations of the genes on a circular chromosome (Figure 1),
- stylize the visual representations of individual genes to make the operator sites visible (Figure 2),
- make the random motion and decay of the individual proteins explicit, and
- show the change in activity rate for each gene as a result of the network dynamics.

Figure 1 shows a screenshot of the visual representation of a GeneVis simulation. The large circle in the middle of the screen represents the chromosome. The filled circles located on the chromosome are the genes, and the small coloured particles, which are spread throughout the grid, represent the proteins. This protein representation is created as a texture mapped square in which the colour is saturated in the center and attenuated towards the edges. This attenuation gives the proteins a fuzzy circular appearance. We will refer to these as discs. The attenuation keeps the proteins visually distinct as they move around the environment. The colour of the disc signifies which protein type it represents, and can be set by the user. For each time step of the simulation, all protein positions and life spans are updated. Furthermore, genes are activated or deactivated depending on regulatory proteins that are in their proximity, and according to their binding rules.

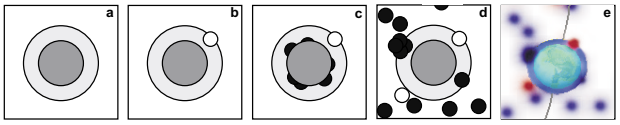

Figure 2: (a) an inactive gene, (b) a gene with a bound regulatory protein, (c) a gene beginning to express proteins (d) a gene continuing to express (e) an actual screen shot of the gene expressing

Figure 2 is a diagram of GeneVis's visual representation of a gene. A gene is displayed as two concentric circles (Figure 2(a)). The outer circle represents the gene's operator site(s). Proteins can attach anywhere on the outer circle and are then bound to an operator site. For example, Figure 2(b) shows one regulatory protein bound to an operator site. When the appropriate activator protein is bound, the gene expression is increased, which results in the increased production of its gene product (Figure 2(c)). The resulting proteins emerge from within the inner circle and start to spread using random motion (Figure 2 (c), (d), and (e)). Rapid dispersement of the individual proteins takes place once they have been released, and they intermingle with the different proteins as they move throughout the environment (Figure 1).

A strength of this dynamic visualization is that interactions between genes and proteins can be seen as they occur in the simulation. For instance, a protein bound to a gene's operator site is

visible, as is the change in activity that results when a required promoter protein binds to a gene. One can see the burst of genetic activity and the resulting release of new individual proteins into the environment.

The genetic network dynamics are visualized as the simulation proceeds. The simulation and visualization can be paused or restarted at any time. The coupling of the simulation and visualization allows for interactive network construction and debugging of network dynamics (for additional information see [1]).

3.2 Protein Concentration Representation

The genetic network dynamics can also be visualized in a more macroscopic manner, by showing protein concentrations, rather than the position of individual molecules. Thought of in this way, the probability of a gene's expression being affected increases and decreases with the chemical concentration of the required proteins.

In terms of genetic dynamics, the simulation becomes much more interesting once proteins have increased sufficiently in number and have spread throughout the environment. When viewing the individual proteins, it can be difficult to gauge whether the proteins have dispersed throughout the entire system. The concentration visualization of the simulation can be used to more readily visually identify when the protein concentrations have increased and become approximately uniform. In GeneVis the simulation can be represented as individual proteins, as concentrations, or at varying representations levels that exist in-between. Concentrations show the spread of the proteins present, thus providing a more general view of the system dynamics.

In the protein interaction representation each protein molecule is represented as an attenuated disc. Conceptually, the protein concentration representation is created by using a larger single attenuated disc to represent several protein molecules. The size of this disc visually covers the same area as the proteins it represents. This attenuated disc is centered at the location of one of the proteins it represents. The rest are not drawn.

Figure 3, top image, shows the protein interaction representation, Figure 3, middle image, shows the protein concentration representation at the same point in a simulation. Notice how with the protein interaction representation it is hard to tell if the proteins are uniformly distributed. This is more readily apparent in the protein concentration representation. In Figure 3, middle image, one can see that that proteins are coming close to having spread through the whole environment. Additionally, the protein colours can be adjusted so that only one protein type is displayed. This allows one to see when specific protein types are dispersed, as illustrated in Figure 3, bottom image.

3.3 Representational Transition

Many visual representations of complex data or concepts are possible. For instance, the concept of a number can be represented in many forms such as binary or decimal. Both of these representations are valid and useful, however the decimal representation makes information about powers of ten more accessible, while the binary representation makes information about powers of two easier to find [11]. Similarly, when we create visual representations as part of our visualization process it is our intention to reveal particular aspects of the data. In the previous sections we presented two visual representations of genetic regulatory dynamics: protein interaction and protein concentration.

Representational transition provides varying degrees of detail within the simulation visualization. The detail is varied from individual proteins, in which 100% of proteins are drawn individually,

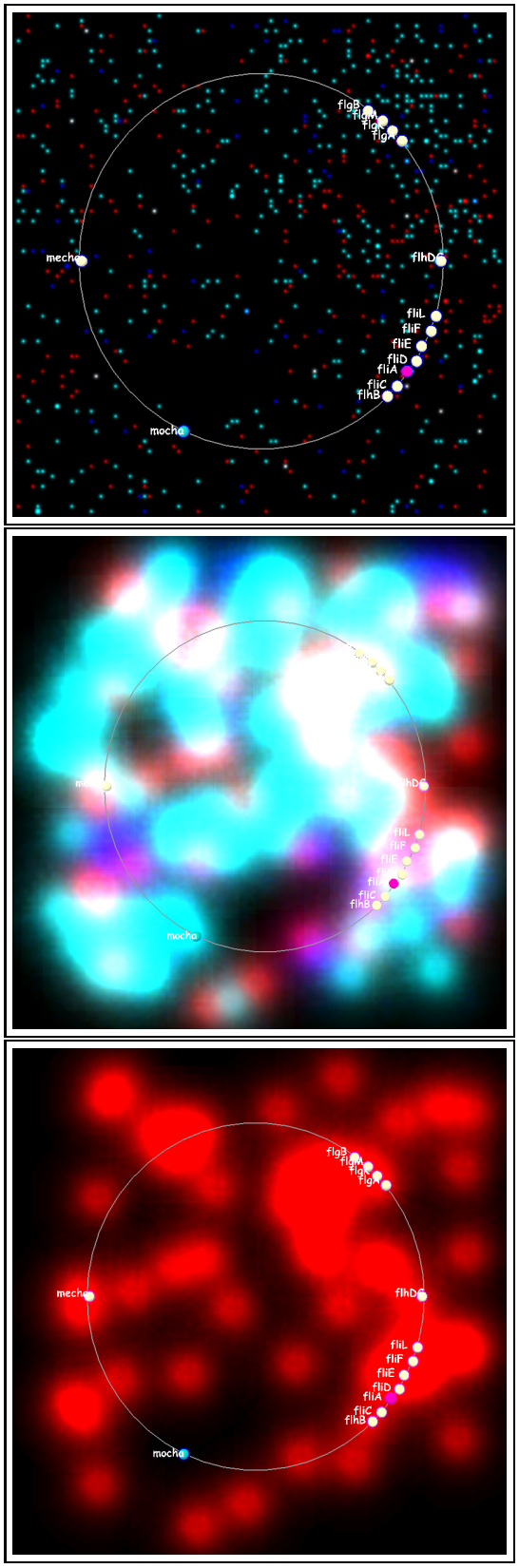

Figure 3: Top, protein interaction representation, middle, protein concentration representation; bottom, protein concentration representation for one protein type

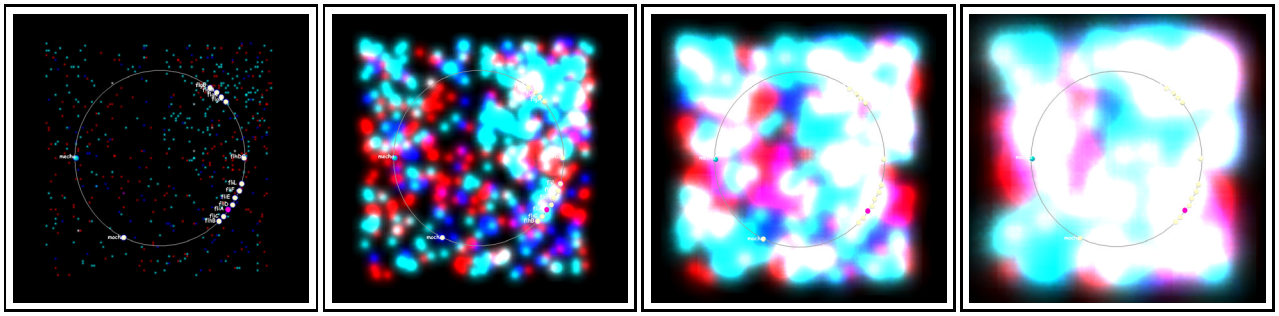

Figure 4: Representational Transformation: (a) *Protein View*: 100% displayed, with individual proteins viewable, (b) *Transition View*: 65% displayed, with small concentration discs viewable, (c) *Transition View*: 35% displayed, with larger concentrations discs viewable, (d) *Concentration View*: 1.56% displayed, with concentrations viewable

each as its own disc, to general concentrations, in which each disc represents many proteins. Figure 4, left, shows the *protein interaction view*, in which individual proteins are displayed. This view is equivalent to the representation in Figure 1. Figure 4, right, shows the *protein concentration view*. In reverse order, changing from the concentration representation to the interaction representation, the attenuated discs that represent groups of proteins become smaller until they represent individual proteins. In Figure 4 this reverse direction can be seen from right to left. Representational transformation is created by changing the size of attenuated discs, the number of proteins a disc represents and the number of discs shown. The attenuated disc's size covers the same area that the proteins it represents would cover.

Displayed	**Proteins represented by single disc**	**Relative disc size**
100%	1	1.0
50%	2	2.0
25%	4	4.0
12.5%	8	8.0
6.25%	16	16.0
3.125%	32	32.0
1.56%	64	64.0

Table 1: Representational transition: this table shows how the percentage transformed relates to the number of proteins represented by an attenuated disc and the size of that disc

Table 1 shows how the representational transition between protein interaction representation and protein concentration representation is calculated. As the number of proteins represented by each disc increases the number of discs decreases. For a protein interaction representation, one protein is represented using one disc with a relative size of 1.0. At 50% displayed, two proteins are represented using one disc with a relative size of 2.0. At 25% displayed, four proteins are represented using one disc with a relative size of 4.0. This is continued on until reaching a cap of 1.56%, where 64 proteins are represented using one disc with a relative size of 64.0. This cap is used to prevent representations that contain too few large discs for lower concentrations.

Whether a disc represents a single protein or a group of proteins it is positioned according to its center. A disc representing a single protein is placed according to that protein's position in the

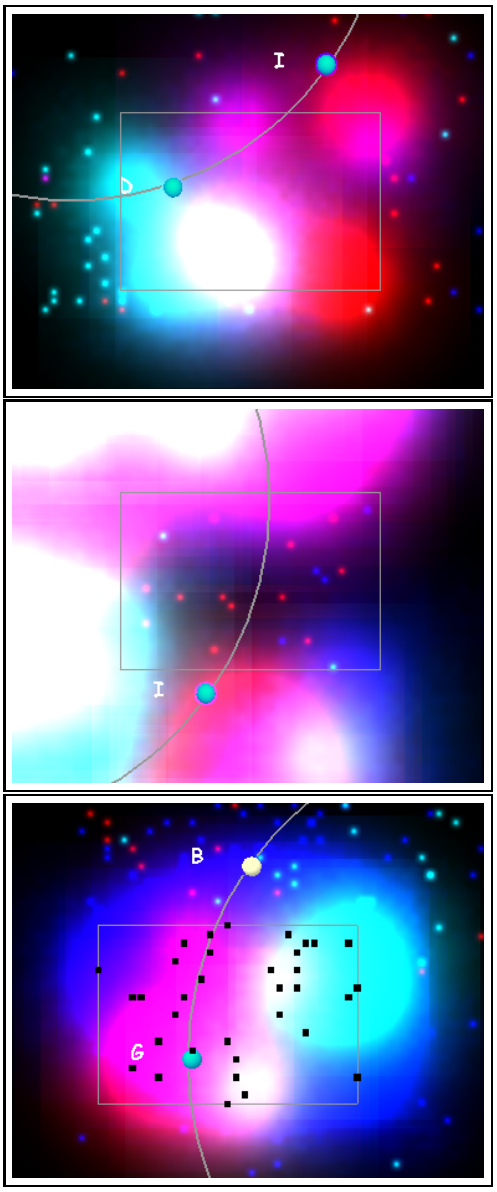

Figure 5: Fuzzy Lenses: (Left) *Concentration Lens*, (Middle) *Protein Lens*, (Right) *Dual Lens*

simulation. The location of discs that represent multiple proteins is resolved as follows. Each disc is centered at the location of one of the proteins it represents. This location is chosen from the locations of the proteins that have been alive in the simulation for the longest. The longest-living protein's positions have been most often randomized, making this position the most representative of the protein spread in the environment. Since we are taking a subset of location coordinates from a randomly distributed set of coordinates, the subset will also be randomly distributed throughout the area to which the proteins have dispersed in the simulation. Since these larger polygons are located randomly, they can overlap. This overlapping causes RGBA disc colors to add. If the added values exceed the maximum they are clamped to the maximum.

3.4 Fuzzy Lenses

Fuzzy lenses have been implemented in GeneVis to provide access to alternate representations in different areas of the visualization. Lenses [2, 3, 9] are variable sized regions that can be moved over the visualization to reveal different information.

There are three Fuzzy Lenses available: a *concentration lens*, which provides a concentration view of the simulation (Figure 5, top), a *protein lens*, which provides the individual protein view of the simulation (Figure 5, center), and a *dual lens*, which shows both the concentration view and the individual proteins (Figure 5, bottom). Each lens is defined over a viewable region in which the lens's representation type is enforced. The regions are movable and resizable, so that any area of the visualization can be viewed within the lens (Figure 5). The lenses are *fuzzy* in that the discs that represent the proteins are allowed to overlap the lens' borders. If discs that happened to be near the edge of a lens were cropped, the resulting visual impression of concentration would be affected. Drawing the discs fully, according to their central location resolves this. Since the discs are semi-transparent, the alternate representation on the other side of the lens boundary is also visible (Figure 5). With the exception of their fuzzy edges these lenses relate directly to the concepts presented as Magic Lenses [2] in that an alternate representation or a combined representation is shown within the lens.

3.5 Base Pair Lens

GeneVis simulates genetic networks for prokaryotic organisms. In these organisms a chromosome is a flexible loop. In GeneVis, this is represented as a circle. The genes in the network are located on this circle according to their base-pair coordinates [5]. Within the chromosome, genes with related functions may be grouped closely together [5]. When genes with close base-pair positioning are visualized within GeneVis, their representations may overlap due to limited resolution (Figure 6, left image). In addition to the visual crowding, the overlapping of operator sites can adversely affect the simulation. To rectify this problem, GeneVis includes the *Base-pair Lens* that allows the user to interactively separate the genes and then proceed with the simulation.

The base-pair lens consists of four sliders. In Figure 6, left image, the handles for these four sliders can be seen as black triangles above, below, to the left and to the right of the chromosome circle. Moving a handle stretches and compresses the adjacent regions of the chromosome circle. Alternatively, moving a handle with the right mouse button can alter the base-pair range that is affected. This allows the users to localize the stretching action to the sections of the chromosome where clustering is most prominent.

Figure 6 shows the network of *Escherichia coli K12's* flagella system with the genes in their base-pair positions [7]. Note that on the right side of the left image there are two areas of the chromosome where genes are closely clustered. Moving the top handle to the left will expand the top right-hand quarter of the circle and compress the top left-hand quarter. The right image of Figure 6 shows how the black handles reflect the genes' new positions, which have now been distributed more evenly.

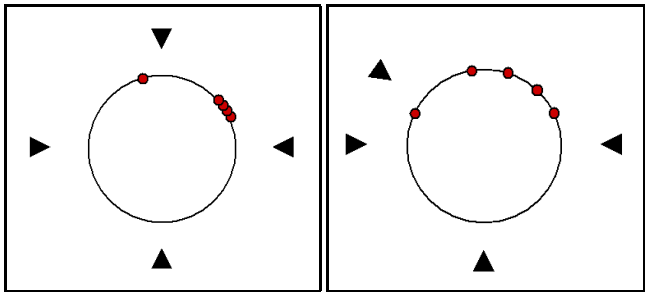

Figure 6: Base-Pair Lens: (Left) Genes in their original base-pair position with clustering on the left side of the chromosome, (Right) Genes distributed evenly through the chromosome with no occlusion

4 Visualizing the Genetic Network Structure

Visualizing the simulation in progress allows the user of GeneVis to examine the genetic network dynamics and compare the simulation results to actual wet-lab experiments. However, biologists are also concerned with the way interactions between genes and proteins form the structure of a genetic network. This type of information is not apparent in either the protein interaction or the protein concentration views. Consequently, a visualization has been specifically designed that displays the genetic network structure by showing regulatory connections between genes through directed graph layouts. This section describes this structural visualization.

The network structure displayed always reflects the structure of the network that is currently simulated. The behavior of the genes and proteins can be interactively adjusted, thus the network organization is calculated by analyzing gene-protein interaction during the simulation. Every gene is checked for the earliest time in which a regulatory protein binds with it and affects its activity level. This is used to place that gene within its appropriate level.

When viewing the dynamics of the network, sometimes a relative hierarchy can be seen in the early stages of the simulation. In this partial hierarchy, genes are grouped according to the proteins that regulate them. For example, gene-protein interactions of the flagella system of *E. coli* have been identified, and one method of illustrating these interactions is shown in Figure 7 [7]. The spatial organization of this diagram is based on the hierarchy of gene expression. Each row holds the genes that have common regulators. The topmost gene is the first to express. The genes in the second row require a regulatory protein from a gene in the previous row to express. These levels can define significant points in the operation of the genetic network, and often have a specific purpose within the organism, for example building a particular section of the organism [7]. Given the significance of these levels, one goal in creating the network structure visualization was to make them explicit.

In the structural visualization, the regulatory relationships to be represented include: forward promoting and inhibiting relationships, backward promoting and inhibiting relationships, and within-level and self-loops both promoting and inhibiting. The forward relationships are those in accord with the level structure of the network. The backward relationships or feedbacks occur when a gene's activity results in the production of a protein that regulates

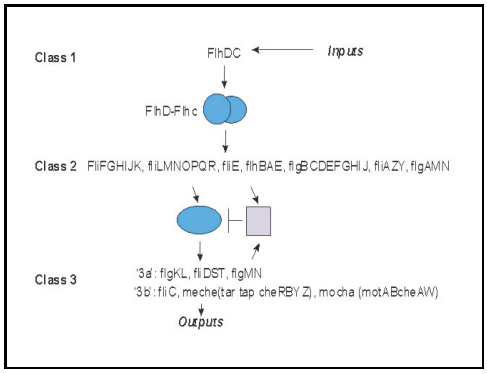

Figure 7: Gene network hierarchy of the flagella operons in *E. coli*. Genes are represented as character strings (e.g. flhDC), with lines in between representing the proteins that relate the genes. There are three levels of genes in this network (adapted from [7])

a gene located at an earlier level. The within-level relationships are those in which a gene's activity affects other genes in the same level. Self-loops are those relationships in which a gene produces a protein that regulates the expression of that gene. These different types of regulatory relationships frequently make the network non-planar, and their presence often interferes with the ease of displaying genetic networks using 2D graph layouts. Graph layouts can very quickly become hard to read when they include multiple edge-crossings [15].

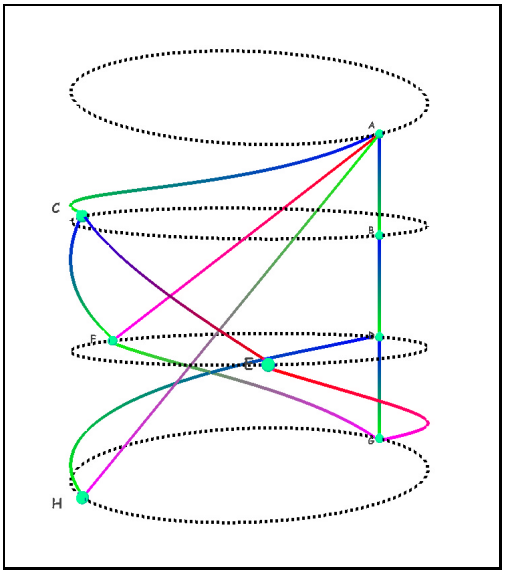

Figure 8: An example of the genetic network structure visualization: Each ring represents a level in the gene hierarchy. The genes (spheres) are related by lines representing regulatory proteins. Forward, backward, and within-level lines are drawn blue, magenta, and yellow at the producing end. At the receiving end all promoting connections fade to green and all inhibiting fade to red.

To address the difficulties of displaying feedbacks, GeneVis presents the genetic network structure in 3D. The network is drawn with the nodes representing genes and the edges representing the relationships between genes. Each level of the hierarchy is transformed from a 2D row of Figure 7 to a 3D ring, and the genes within that level are distributed evenly around the ring (Figure 8). The rings are indicated by dashed lines to keep them visually distinct from the network connections.

Forward protein regulation connections are displayed as curved lines. Feedbacks are shown as straight lines. Within-level relationships are drawn around the ring. Self-loops are small loops starting and ending at the same gene. Colors are also used to indicate the direction and type of the relationship. The forward regulation line is blue at the producing end, the backward regulation line is magenta at the producing end, and the within-level line is yellow at the producing end. All lines with promoting connections fade to green at the receiving end, and to red if they inhibit the expression of the genes they control. Making the different types of regulation visually distinct in both color and shape alleviates some of the edge-crossing problems common to graph layouts. To take advantage of the 3D layout, the entire network can be rotated, giving the user different views of the network architecture.

4.1 Visual Integration of Network Structure

To visually integrate the simulation and the network structure, the transition between the two visualizations can be animated. This animation can be viewed at once or stepped through in either direction.

Figure 9 shows steps of this animation, moving from the simulation to the network structure visualization. The purpose of this animation is to allow a user to track a gene from its location in the simulation to its location in the network structure visualization. In the first step of the transition, the lines that represent the regulatory connections are drawn on the circular chromosome of the simulation visualization (Figure 9, first image). Next, each level is drawn inward, one by one, until the network is partitioned into levels (Figure 9, second image). At this point, the network is represented as a series of concentric rings in a 2D plane. The next stage of the transition (Figure 9, third image) moves the viewpoint, to give a side view. Then each ring is translated upwards, showing each level and its connections (Figure 9 fourth image). At the end of the animation, Figure 9, last image, shows all the rings enlarged to the same diameter and the forward connections changed to curves. Each transition takes place gradually to allow the user to track individual genes from one step to the next.

4.2 Ring Lens

As the network size increases, the level rings become closely packed together. This congestion can make connections between the genes difficult to discern. The *Ring Lens* addresses this problem. It is a type of detail-in-context lens, which increases the space for the viewing of details in the selected region while maintaining the surrounding context. To this end, the Ring Lens enlarges the diameter of the selected rings and spreads them vertically. The new position and diameter of the ring is calculated as follows. First, a parameter called *PositionRatio* is calculated for each ring according to this formula:

If $(Ring > LensCenter)$

$$PositionRatio = \frac{(Top - Ring)}{(Top - LensCenter)} \quad (1)$$

else

$$PositionRatio = \frac{(Ring - Bottom)}{(LensCenter - Bottom)}, \quad (2)$$

Here *Ring* is the vertical position of the ring to be adjusted and *LensCenter* is the vertical position of the Ring Lens, *Top* is the

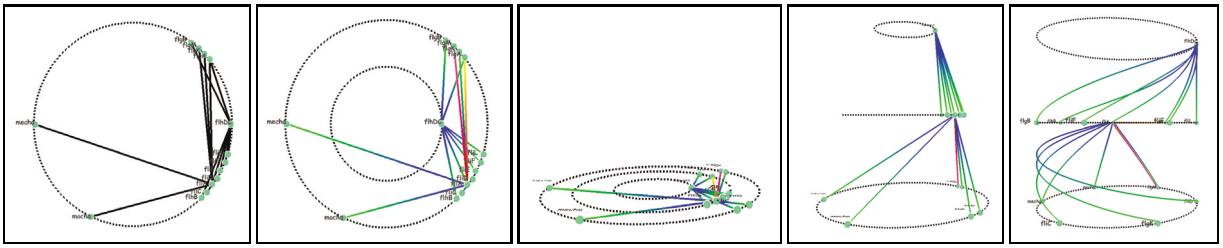

Figure 9: Visual integration that moves the user from the simulation visualization to the network structure visualization

position of the topmost ring and *Bottom* is the position of the lowest ring. *PositionRatio* is used to calculate the change in ring diameter:

$$scaleDiameter = (PositionRatio^2 * (MaxMag)) + 1.0, \quad (3)$$

Squaring the *PositionRatio* makes the amount of magnification drop off more quickly. Adding 1.0 ensures that the ring's diameter does not diminish. *PositionRatio* is also used to calculate both the new vertical location of the ring. To this end, the parameter *VerticalAdjust* is calculated with the formula:

$$VerticalAdjust = \frac{PositionRatio^2 * (Top - Bottom)}{VerticalScaleFactor} \quad (4)$$

and *VerticalAdjust* is subtracted from *Top* if the ring is above the lens center, and added to *Bottom* if it is below the lens center. Figure 10 is a diagram that shows how the ring lens works.

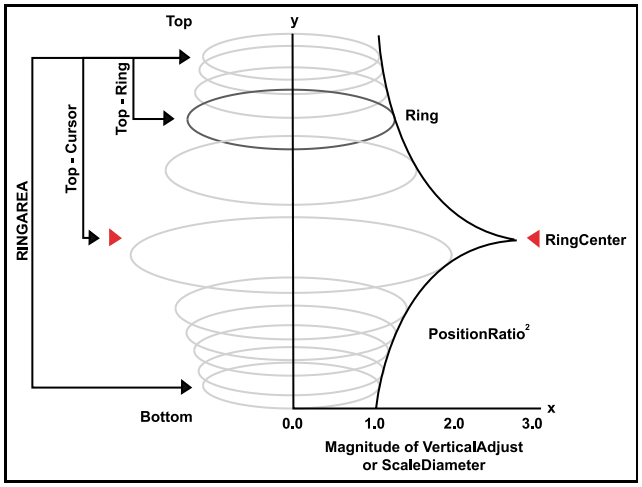

Figure 10: Diagram of the *Ring Lens* distortion function

The vertical position of the Ring Lens is controlled by the mouse. Figure 11 shows screen shots of the Ring Lens in different positions. The left image shows the Ring Lens placed at the second level ring, causing it to be enlarged in diameter. The middle image shows the lens shifted towards the bottom of the view. This makes the connections between the lower two level rings more visible by increasing the amount of space between them. The right image shows the lens near the top of the view this time opening up the space between the first two levels. The Ring Lens allows the user to interactively view the selected levels within the genetic network structure while maintaining the context of all the other rings.

5 Conclusions and Future Research

In this paper we have presented GeneVis, an interactive simulation and visualization environment that has been developed for the exploration of genetic regulation networks. GeneVis provides dynamic visualizations of simulated genetic network behaviour and a visualization of the network structure. It supports three visual representations. The protein interaction representation shows the dynamics of the simulated network behaviour through the motion of individual proteins. The protein concentration representation depicts the concentrations of proteins during the simulation. The network structure representation shows the dependency structure of the genetic network using a 3D graph layout. This representation shows several types of regulatory relationships, including forward, backward, and self regulation. All of these can have either promoting or inhibiting effects.

GeneVis also provides several specialized viewing tools and techniques. These include:

- The continuous representational transformation between the protein interaction representation and the concentration representation.
- The three Fuzzy Lenses, which allow one to view selected regions of the simulation dynamics with the representation of choice.
- The Base-Pair Lens, which allows one to reposition the genes, thus separating and more evenly distributing closely clustered genes.
- The animated transition between the dynamic visualizations and the network structure visualization.
- The Ring Lens, which provides detail-in-context viewing for the network structure.

With these representations and tools, genetic regulation networks can be viewed and explored.

There are many possible future directions for this research. Some of the visualization directions include: making a visual front end that would allow a user to edit the network structure, continuing to improve the network structure visualization in order to further clarify the structure, and providing a magnification lens for the dynamic visualizations. Also, gene expression graphs could be plotted in real-time for precise measurement of when equilibrium or constant expression levels are reached.

6 Acknowledgments

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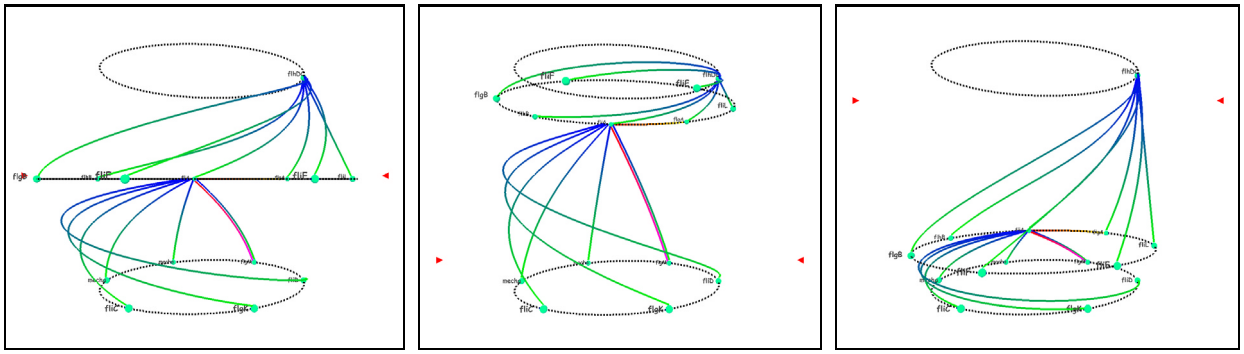

Figure 11: Ring lens view transformation

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