Robustness in Modular Networks

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1 Background and Motivation

In the contemporary field of Systems Biology, it is widely accepted that the combination of modularity and network motifs within biological systems lend organisms an advantage when interacting with their environment [1,2]. The former is defined as "the separability of [a] design into units that perform independently" [1]. These units are typically composed of a set of "interconnected edges", always lying within a larger network of nodes. A biological example of modularity is found in the organically ubiquitous process of chemotaxis. Generally viewed as the movement of a cell either towards or away from some sort of chemical signal [3], chemotaxis requires a myriad of smaller functions performing synchronously to effectively respond to chemical indicators. The cell must be able to sense the signal, compute the direction of motion, move to and metabolize the signal, and communicate with other cells, in addition to a number of other functions. Cells have evolved gene modules to achieve these functions, such as motor modules and communication modules that can perform independently of one another. These modules have been able to adapt and evolve to face changing environments over time, sensing and responding to the plethora of signals that they now regularly encounter. Many of these modules are exhibited across the wide range of biological domains, creating cross-species patterns that are easily recognizable by researchers. These patterns are known as network motifs, with some of the most prevalent being feed-forward loops and diamond patterns [1], common staples of both biological and computational networks. Network motifs, like modules, are composed of sets of nodes and edges, whose inter-connectivity determines their function. Motifs and modules are similar, for motifs can be modules and certain modules can indeed be motifs. Both play important roles in the field of Systems Biology.

The importance of modularity and motifs to biological systems is illustrated by the behavior of simulated computational systems. Several separate experiments have shown that modularized artificial systems perform better than their un-modularized, randomly generated counterparts at solving various goals [1,2]. Not only are they able to solve goals more effectively, but the modularized systems were able to solve them more quickly and even "remember" how they were solved. One hypothesis for their enhanced performance is based on the principle of robustness; as evidenced by chemotaxis, modularity allows cells to respond to a wide range of signals efficiently, as opposed to responding to only a few signals near perfectly. This robust performance translates to improved problem solving abilities both in nature and in artificial systems, even if some optimization is sacrificed. While the randomized networks in the studies were able to solve a single goal adequately, sometimes even optimally, they could not solve multiple goals with the same level of competency as modularized systems. Modularity also served as a form of memory for these systems; the systems had the ability to recognize subproblems within the overall goal, and they would create a module to solve the subproblem. If the subproblem was encountered later, the system could refer back to the original module it created.

In nature, most organisms must be capable of meeting multiple challenges without completely altering their methodology, lest they perish. For example, the generation of energy within a human varies depending on the fuel available; carbohydrates require a different digestion process than lipids or proteins, despite all serving as equally vital fuel sources for human cells. Humans have developed modules that can robustly digest these different nutrients effectively, with many cells equipped with multiple modules. This is more practical and economical than the non-modular alternative, where one cell can only digest one type of nutrient. Sacrificing optimization for the robustness afforded by modularity appears to be a common theme across biological systems, as the latter provides an advantageous toolkit capable of meeting a variety of problems.

This article is inspired by another article, The Architecture of Complexity, written by Simon. Although written over sixty years ago, many of its claims regarding Systems Biology have yet to be disproven. In particular, Simon discusses how systems that are modular in nature are better equipped to withstand outside, environmental interruptions. In addition to this claim, Simon describes in detail the early functionalities of systems and their importance to the study of biology. Though his assumptions were slightly misguided, Simon's article laid the foundation for much of the study in contemporary systems biology, and serves as inspiration for this paper.

2 Aims of Study

This study aims to authenticate the findings of previous papers, predominantly those of Simon, in addition to those by Kashtan and Alon, and Clune and Lipson. Specifically, this study aims to show that a modular network will produce an output faster than the random network, the primary reason being that it can move through the nodes in a more orderly fashion due to its internal structure. This idea of responsive output has implications in countless biological systems, primarily in signal cascades, which are generally present in many types of biological reactions. This study models networks such that they represent a type of signal cascade that culminates in the activation of a gene. Generally, the faster a system can generate a response, the better an organisms chances at overall survival. The time it takes for the gene of interest to be activated, denoted as the overall output, is modeled in each network. This study generates two major types of networks: those that are intentionally modular, and those that are generated randomly with no modularity exhibited.

Upon generating these models, this study aims to show the output of the modular networks are more responsive to changes in the parameters and initial conditions than the random networks. Modular networks should be more stable to changing conditions than random networks due to their innate robustness, and therefore will ideally exhibit increased levels of responsiveness. The input parameters β, α, n, and k are each changed one at a time and the resulting outputs of the modular and non-modular systems are compared. These values represent various characteristics in the proteins involved in the signal cascade that can organically change due to mutation within a species, such as the activation of a gene. β represents the production rate of the system, or how much total positive input is received. α represents the degradation rate of the system; most types of organic matter involved in nearly all biological reactions do not last forever, due primarily to their finite half life, a value represented by their degradation rate. The n value represents the Hill coefficient in the systems of equations and determines the sharpness of the input function. The final value that will be changed, k, represents the activation threshold for a system. That is, how much positive input β is required before the system can be activated and exhibit growth, or in this case, the propagation of signals to subsequent nodes. The equations will also changed to represent OR gates instead of AND gates, and vice versa. In systems biology, AND and OR gates act as methods to control networks that are exhibited in both organic and computational systems. AND gates require two signals to be received by a given node in order for the signal to continue through the signal cascade. OR gates, on the other hand, require only one signal to be received by a node in order to propagate the signal cascade. The study looks at the magnitude of the changes experienced by the systems, not just whether the gene turns on or off. This change in output magnitude will represent an increase or decrease in the transcription rate of the the gene. These changes will then be quantified to provide a comparison between the output results of modular and non modular networks. Higher levels of responsiveness therefore correlate to increased levels of gene transcription, a potentially very advantageous characteristic for organisms.

By quantifying the changes experienced by the modular and random networks, this study can determine if the modular networks are able to respond to changes more efficiently and effectively than their random counterparts, thereby either confirming or disproving this study's hypothesis. If the hypothesis is correct and the modular system is able to respond more quickly, it will confirm the findings of Simon, Kashtan and Alon, and Clune and Lipson. This study aims to substantiate their findings, as there are few studies in contemporary systems biology that do so. The confirmation of their findings will provide researchers within the field of systems biology further evidence as to the power and effectiveness of modularity . If this experiment fails to support the original hypothesis, this study will need to be performed again with different parameters in order to establish concrete evidence that can substantiate a conflict with previous findings outlined in the papers above.

3 Methods

For this study, we created four different networks. One of which was a modular network consisting of a start node, 4 incoherent feed forward loops, and an end node. The other three networks were randomly generated. The modular network and an example of the random network are shown in 1.

Each network has 14 nodes total, including the input and output nodes. The random networks are created with the stipulations that they must have a matching amount of edges and average degree as the modular network in order to do a fair analysis. These random networks are created as null models to show that modular networks will behave differently than non-modular networks and are made in triplicate to emphasise that these characteristics cannot be reproduced by chance alone. To produce the output, each system must go through every node as well as not having any 'dead end' paths that are not the end node of interest. After the networks are created we will derive equations to represent them in order to perform analysis on them.

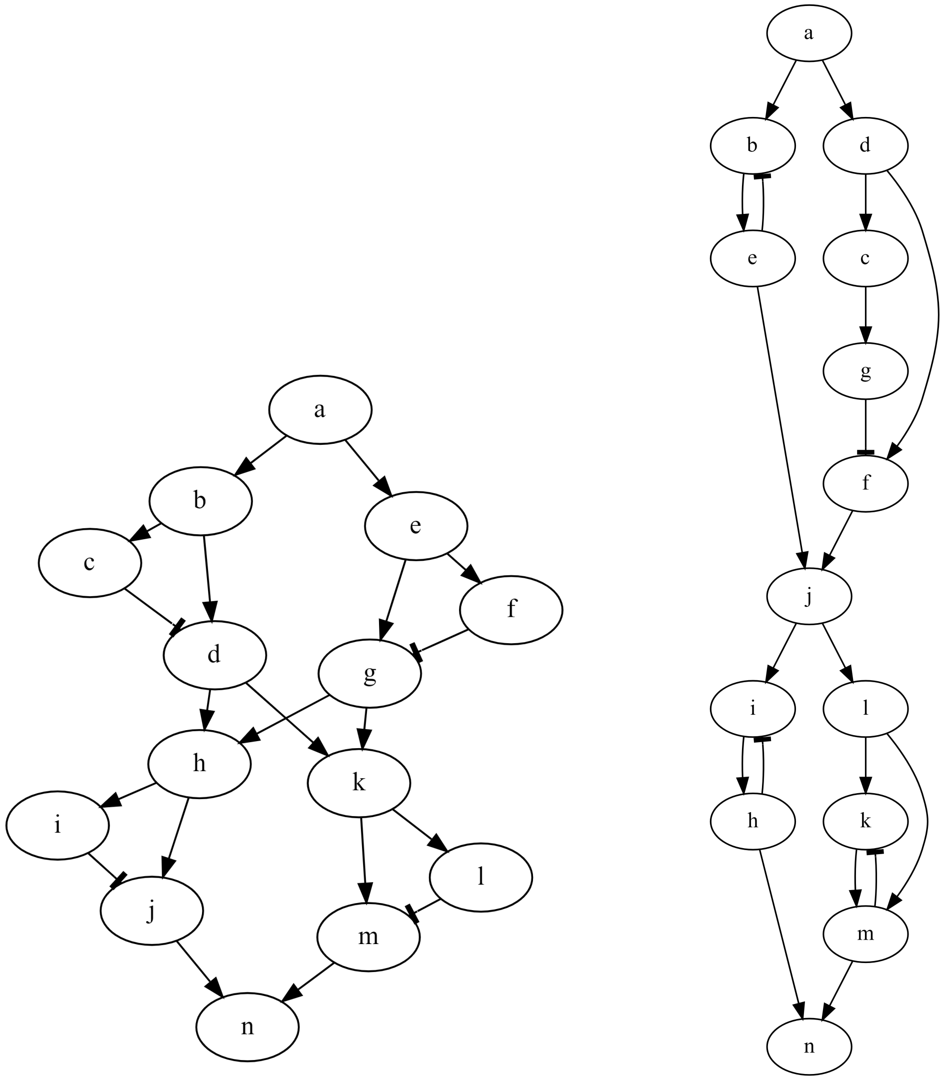

Figure 1: The network on the left is the random network that was worked with. The network on the left is an example of one of the random networks (random network 1). The other two random networks are included in Supplemental Materials.

We then began to try to simulate evolution through these networks with the use of the python package PyGad. However, this package required us to derive an objective function for our terminal node, node n. Beginning this process led us to the equation below for node d in our modular network. Because of how fast the objective functions became complicated, we decided to take a different approach to our project in order to not derive the functions for n for all four networks that we created.

$$d = \frac{\beta_d\alpha_d K_{cd}^{n_d}(\frac{\beta_b\alpha_b a^{n_b} - \beta_b\alpha_b a^{n_b} e^{\alpha_b t}}{K_{ab}^{n_b}+a^{n_b}})^{n_d} - \beta_d\alpha_d K_{cd}^{n_d}(\frac{\beta_b\alpha_b a^{n_b} - \beta_b\alpha_b a^{n_b} e^{\alpha_b t}}{K_{ab}^{n_b}+a^{n_b}})^{n_d} e^{\alpha_d t}}{(K_{bd}^{n_d} + (\frac{\beta_b\alpha_b a^{n_b} - \beta_b\alpha_b a^{n_b} e^{\alpha_b t}}{K_{ab}^{n_b}+a^{n_b}})^{n_c})(K_{cd}^{n_d} + (\frac{\beta_c\alpha_c(\frac{\beta_b\alpha_b a^{n_b} - \beta_b\alpha_b a^{n_b} e^{\alpha_b t}}{K_{ab}^{n_b}+a^{n_b}})^{n_c} - \beta_c\alpha_c(\frac{\beta_b\alpha_b a^{n_b} - \beta_b\alpha_b a^{n_b} e^{\alpha_b t}}{K_{ab}^{n_b}+a^{n_b}})^{n_c} e^{\alpha_c t}}{K_{bc}^{n_c} + (\frac{\beta_b\alpha_b a^{n_b} - \beta_b\alpha_b a^{n_b} e^{\alpha_b t}}{K_{ab}^{n_b}+a^{n_b}})^{n_c}})^{n_d})} \tag{1}$$

For out new method, a system of differential equations was derived for each network using Hill functions. Both repressive and activating connections were considered. First, these equations were created using all AND gates. They were then modified to use OR gates. This created eight networks in total, 2 modular and 6 random. An example of these equations can be seen below, the rest are included in supplemental materials. These equations are for the modular network using AND gates.

$$\frac{\delta B}{\delta t} = \beta \frac{A^n}{k^n + A^n} - \alpha B \tag{2}$$
$$\frac{\delta C}{\delta t} = \beta \frac{B^n}{k^n + B^n} - \alpha C \tag{3}$$
$$\frac{\delta D}{\delta t} = \beta \frac{B^n}{k^n + B^n} \frac{k^n}{k^n + C^n} - \alpha D \tag{4}$$
$$\frac{\delta E}{\delta t} = \beta \frac{A^n}{k^n + A^n} - \alpha E \tag{5}$$
$$\frac{\delta F}{\delta t} = \beta \frac{E^n}{k^n + E^n} - \alpha F \tag{6}$$
$$\frac{\delta G}{\delta t} = \beta \frac{E^n}{k^n + E^n} \frac{k^n}{k^n + F^n} - \alpha G \tag{7}$$
$$\frac{\delta H}{\delta t} = \beta \frac{D^n}{k^n + D^n} \frac{G^n}{k^n + G^n} - \alpha H \tag{8}$$
$$\frac{\delta K}{\delta t} = \beta \frac{D^n}{k^n + D^n} \frac{G^n}{k^n + G^n} - \alpha K \tag{9}$$
$$\frac{\delta I}{\delta t} = \beta \frac{H^n}{k^n + H^n} - \alpha I \tag{10}$$
$$\frac{\delta J}{\delta t} = \beta \frac{H^n}{k^n + H^n} \frac{k^n}{k^n + K^n} - \alpha J \tag{11}$$
$$\frac{\delta L}{\delta t} = \beta \frac{K^n}{k^n + K^n} - \alpha L \tag{12}$$
$$\frac{\delta M}{\delta t} = \beta \frac{K^n}{k^n + K^n} \frac{k^n}{k^n + L^n} - \alpha M \tag{13}$$
$$\frac{\delta N}{\delta t} = \beta \frac{J^n}{k^n + J^n} \frac{M^n}{k^n + M^n} - \alpha N \tag{14}$$

These equations were numerically integrated using Euler's method with $dt = 0.1$min. The starting parameters were set according to 3 seen below.

Starting Parameter Values	
Parameter	Value
β	10 (per minute)
α	2
k	10 (per cell)
n	2

To test the response speed of the networks, an input list was created. At two points, the input is turned on (value is set to ten) and throughout the rest of the list, the input is off (value set to zero). The rest of the nodes were set to zero to start. After numerical integration, the difference between when the input turns on and the peak of the response (node n) was calculated. A graph of the input and the response for the modular network with AND gates can be seen below. The rest of the graphs are shown in Supplemental Materials.

To test the impact of changing parameters, each of the four parameters (β, α, k, and n) was changed one at a time. Three different values for each parameter were tested. Numerical integration was run for each varying parameter. Then, the percent change of output was calculated in relation to the output with the base parameter described in 3.

4 Results and Discussion

The modular networks were consistently faster than the random networks. When AND gates were used, the modular network responded to an input in 1.5 minutes. The graph of these change can be seen in 2.

This was faster than all three of the random networks which responded in, on average, 1.9 minutes. The standard deviation is $6.67 * 10^{-3}$ making the results from the modular network statistically significant with 99% confidence. When OR gates were used, the modular network still responded in 1.5 minutes. However, the time for the random networks to respond increased to an average of 1.97 minutes. The standard deviation is $9.66 * 10^{-2}$. All of the values can be seen in [reference table]. Thus, the results for the modular network are statistically significant at a 99% confidence level. This indicates that modular networks respond faster to stimulus than random networks of the same size. It is interesting to note that changing from AND gates to OR gates did not make a difference in the time to response in a modular network. In the random networks, there was a change observed, but it was inconsistent. Some increased in time while others decreased. They results were fairly similar however and only small changes were observed.

For every parameter that was changed (β, α, k, and n), the modular systems saw a larger increase than the random ones. The average magnitude change for the modular networks and the random networks can be seen in table 4. The raw values are included in the Supplemental Materials, in tables in 7.9.

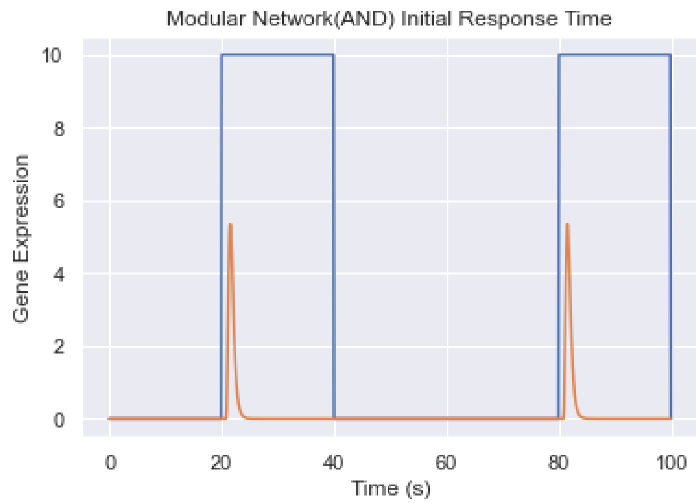

Figure 2: The graph above shows the input to the system (in blue) and the output of the modular network with AND gates (in orange). The parameters used are outlined in 3 It demonstrates a small delay between the input and the output. Since the difference is so small, the graph does not tell much information, and a more quantitative approach was needed. This graph is included as an example. Graphs for all other networks can be seen in the Supplemental Materials.

Average Magnitude of Change		
Parameter Change	Modular Change	Random Change
1.1x increase in β	9.647	1.514
1.2x increase in β	17.025	2.769
2x increase in α	18.891	1.869
3x increase in α	50.775	3.985
5x increase in k	476.31	2650.76
10x increase in 5	453.755	2731.32
2x increase in n	17.630	11.920
3x increase in n	23.41	13.623

For almost every change parameter change, the modular networks saw a larger change in output than the random network. The only exception to this is seen when k is changed. It is important to note that the third random OR gate network seemed to be an outlier. When the point is not considered, the average change for a 5x increase in k is 39.190. Similarly, the change for 10x increase is 40.560. This would make the random networks more stable than the Since the sample size is quite small (only three random networks) it is hard to know if this network is truly an outlier or if other networks would also exhibit this same behavior. It is also interesting that this was only observed when OR gates where used; the same random network with AND gates is similar to the others. This is noteworthy because the AND vs OR gates do not seem to make much of a difference in most situations.

Changing k seems to create different results than changing other parameters. Not only is it the only time modular networks have a lower magnitude change than random networks, both random network 2 and 3 changed much more when OR gates were used

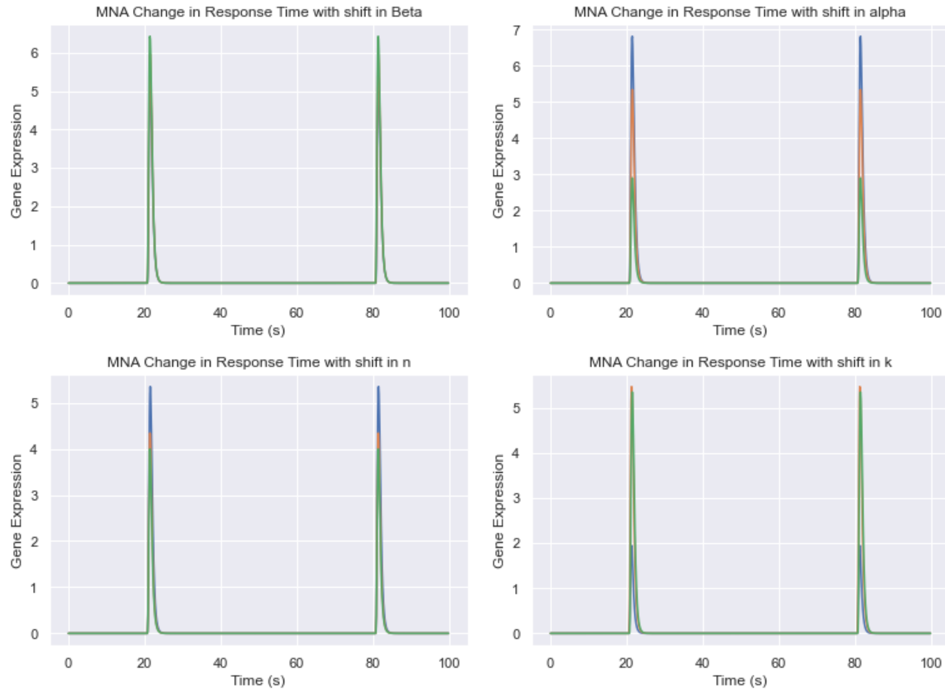

Figure 3: The graphs above show how the output changed for each changing parameter in the modular network for AND gates. The blue line is the initial output with the parameters outlined in 3. The orange line is one increase of a given parameter, and the green line is the second increase of the parameter. Almost no change is observed when β changes just by looking at the graphs. There is a decrease in output observed when both α and n are increased. Increasing k first shows an increase in output. Increasing k again causes the output to decrease from this new value.

than AND gates. Furthermore, in three of the eight networks tested actually decreased when the change of k was increased. When every other parameter was tested, the modular network saw a greater change with AND gates. When k was changed, the opposite was true. It is hard to say why changing k created such weird results. One theory is it's role in both the numerator and the denominator of the hill function. Increasing this parameter would thus increase both numerator and denominator making the results more variable. This would explain why is it less predictable than β or α, however n also plays a role in both numerator and denominator and still behaved more like β and α.

Regardless of this behavior, it seems reasonable to conclude that modular networks are more responsive than random networks to most changing parameters. At first glance, this seems to contradict the conclusions made by [1,2] which states that modular networks were more robust to changes in environment and harmful mutations. However, these papers tested these networks under the concept of evolution. This means they tested thousands of networks and selected the most successful networks to be the parent population of the next generation. If a mutation has a large, negative impact on the output of the network, that network would not be selected as part of the parent generation. This would make the overall population seem more stable as these changes would not be passed down to offspring. If the effect of a single mutation is smaller, it may be passed down as the fitness of this individual organism would be less impacted. An individual modular network is more responsive, as demonstrated by this paper and because of this, a population of modular networks is more robust to negative changes. Conversely, a positive mutation would be more likely selected for if it saw a greater positive impact on output. This is consistent with the findings of previous papers which found that modular populations select for positive mutations at a higher rate. This study does not use a fitness function, so the mutations are considered neither positive or negative. However, the conclusion that modular networks are more responsive to changing parameters is consistent with previous findings.

5 Conclusion

The results of this study indicate that modular systems are much more responsive to input changes than the random, non-modular networks. This was the case for all networks, including those with OR and AND gates. It was also the case for each input variable that was changed in the systems, including α, β, and k. This therefore confirms our hypothesis that modular networks will exhibit increased levels of responsiveness to change within the system. Modularity is displayed frequently in biological networks; organisms have evolved to optimize efficiency within their systems, and modularity allows for increased responsiveness to external, environmental signals. The results of this study provide computational evidence of why modularity is ideal for both simulated and organic systems alike. Systems with modularity, due to its demonstrated increase in responsiveness, will be better equipped to handle environmental changes, which occur often in nature at micro and macro levels.

It is also essential to recognize that this level of responsiveness may not be beneficial for a single organism with respect to mutations. If the mutation is negative, the data supports that the organism will exhibit exaggerated responses to the mutation that may be catastrophic to the organism's survival. Conversely, if the mutation is positive, the organism will likely exhibit a heightened positive response greatly increasing fitness. On the scale of one entity, this seems very 50/50 on surviving a mutation. However, on the scale of a population over billions of years, having strong mutations stand out more and negative mutations never be passed on could greatly expedite evolutionary processes.

6 Path Forward

In future works with this same topic, the systems designed and tested here would be tested again but with more details and variables included. In the name of time and simplicity, the nodes of this system were not given edge weights nor were their connections changed at random. To better mimic a biological system, these concepts should be applied as it is unlikely that two nodes in an observed system would have the exact same interactions. This would add two variables for alteration and testing for their effects on a network and bring this model closer to mimicking biological behavior.

As this project focused on analyzing the responsiveness of modular systems with respect to changing conditions, future work would focus on the robustness of modular systems with respect to mutations on a population scale. It has been seen that modular systems within a population are resistant to the rise of harmful mutations while promoting beneficial ones[2]. To show this, the same systems generated here would be recycled into a new testing format. These systems would be mutated (the mutations represented by changes in edge weights, node connections, and the same parameter values tested here), evaluated for their fitness (defined as the fastest output time), and finally the most fit would be moved to the next iteration of mutations. These mutations would be randomly generated as to what changes and if that change implements positive or negative effects. As modular networks are shown here to be more responsive, the populations possessing modular frameworks would change faster and only the positive changes would be have increased fitness. With enough iterations, this process would theoretically show that populations containing modular networks are more robust to the rise of harmful mutations and promoting to the rise of positive mutations.

Further work related to modularity can test this study's theory on responsivity in a biological setting. For example, quantifying the potential response differences between a cell using modular chemotaxis and a randomly generated computational cell will give insight to whether our results hold true in vivo. This study has shown that modularity increases responsivity in artificial systems, supporting the hypotheses of Kashtan and Alon. While this study only analyzes computational systems, it provides the framework required to investigate the characteristics of biological systems in relation to modularity.

7 Supplemental Materials

7.1 Graphical Depiction of Networks

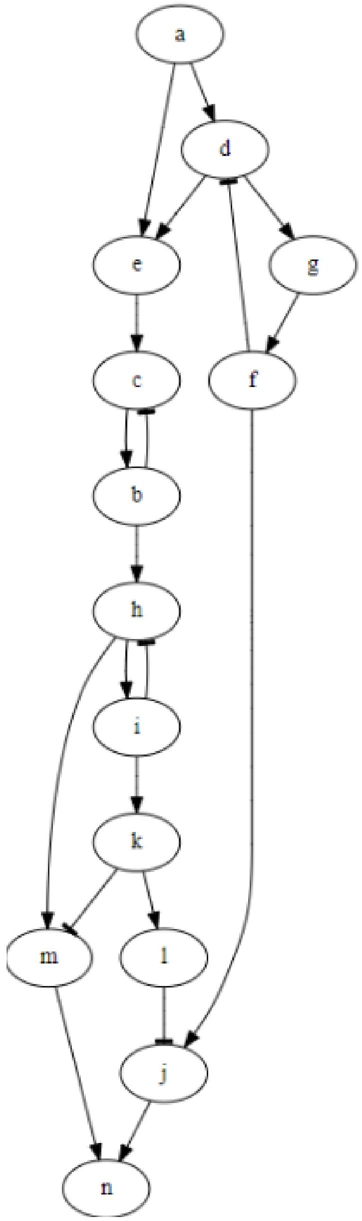

Figure 4: The graph above shows the network used as Random Network 2.

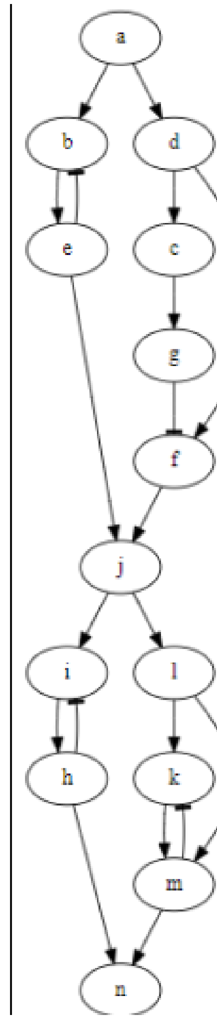

Figure 5: The graph above shows the network used as Random Network 2.

7.2 AND gates–random network 1 equations and graphs

$$\frac{\delta B}{\delta t} = \beta \frac{C^n}{k^n + C^n} \frac{k^n}{k^n + D^n} - \alpha B \tag{15}$$

$$\frac{\delta C}{\delta t} = \beta \frac{I^n}{k^n + I^n} - \alpha C \tag{16}$$

$$\frac{\delta D}{\delta t} = \beta \frac{A^n}{k^n + A^n} \frac{k^n}{k^n + F^n} \frac{k^n}{k^n + J^n} - \alpha D \tag{17}$$

$$\frac{\delta E}{\delta t} = \beta \frac{G^n}{k^n + G^n} - \alpha E \tag{18}$$

$$\frac{\delta F}{\delta t} = \beta \frac{G^n}{k^n + G^n} - \alpha F \tag{19}$$

$$\frac{\delta G}{\delta t} = \beta \frac{A^n}{k^n + A^n} - \alpha G \tag{20}$$

$$\frac{\delta H}{\delta t} = \beta \frac{I^n}{k^n + I^n} \frac{k^n}{k^n + B^n} - \alpha H \tag{21}$$

$$\frac{\delta I}{\delta t} = \beta \frac{J^n}{k^n + J^n} - \alpha I \tag{22}$$

$$\frac{\delta J}{\delta t} = \beta \frac{L^n}{k^n + L^n} - \alpha J \tag{23}$$

$$\frac{\delta K}{\delta t} = \beta \frac{J^n}{k^n + J^n} - \alpha K \tag{24}$$

$$\frac{\delta L}{\delta t} = \beta \frac{E^n}{k^n + E^n} \frac{F^n}{k^n + F^n} - \alpha L \tag{25}$$

$$\frac{\delta M}{\delta t} = \beta \frac{L^n}{k^n + L^n} \frac{K^n}{k^n + K^n} - \alpha M \tag{26}$$

$$\frac{\delta N}{\delta t} = \beta \frac{H^n}{k^n + H^n} \frac{M^n}{k^n + M^n} - \alpha N \tag{27}$$

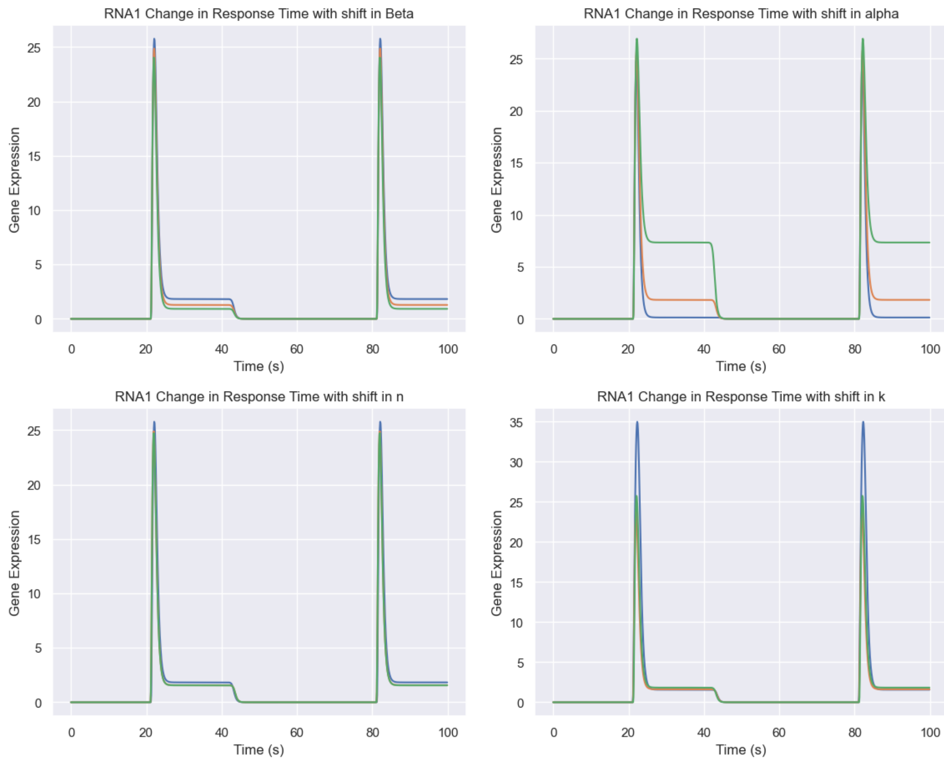

Figure 6: Changing parameters graphs for the Random Network 1 with AND gates

7.3 AND gates–random network 2 equations and graphs

$$\frac{\delta B}{\delta t} = \beta \frac{C^n}{k^n + C^n} - \alpha B \tag{28}$$

$$\frac{\delta C}{\delta t} = \beta \frac{E^n}{k^n + E^n} \frac{k^n}{k^n + B^n} - \alpha C \tag{29}$$

$$\frac{\delta D}{\delta t} = \beta \frac{A^n}{k^n + A^n} \frac{k^n}{k^n + F^n} - \alpha D \tag{30}$$

$$\frac{\delta E}{\delta t} = \beta \frac{A^n}{k^n + A^n} \frac{D^n}{k^n + D^n} - \alpha E \tag{31}$$

$$\frac{\delta F}{\delta t} = \beta \frac{G^n}{k^n + G^n} - \alpha F \tag{32}$$

$$\frac{\delta G}{\delta t} = \beta \frac{D^n}{k^n + D^n} - \alpha G \tag{33}$$

$$\frac{\delta H}{\delta t} = \beta \frac{B^n}{k^n + B^n} \frac{k^n}{k^n + I^n} - \alpha H \tag{34}$$

$$\frac{\delta I}{\delta t} = \beta \frac{H^n}{k^n + H^n} - \alpha I \tag{35}$$

$$\frac{\delta J}{\delta t} = \beta \frac{F^n}{k^n + F^n} \frac{k^n}{k^n + L^n} - \alpha J \tag{36}$$

$$\frac{\delta K}{\delta t} = \beta \frac{I^n}{k^n + I^n} - \alpha K \tag{37}$$

$$\frac{\delta L}{\delta t} = \beta \frac{K^n}{k^n + K^n} - \alpha L \tag{38}$$

$$\frac{\delta M}{\delta t} = \beta \frac{H^n}{k^n + H^n} \frac{k^n}{k^n + K^n} - \alpha M \tag{39}$$

$$\frac{\delta N}{\delta t} = \beta \frac{J^n}{k^n + J^n} \frac{M^n}{k^n + M^n} - \alpha N \tag{40}$$

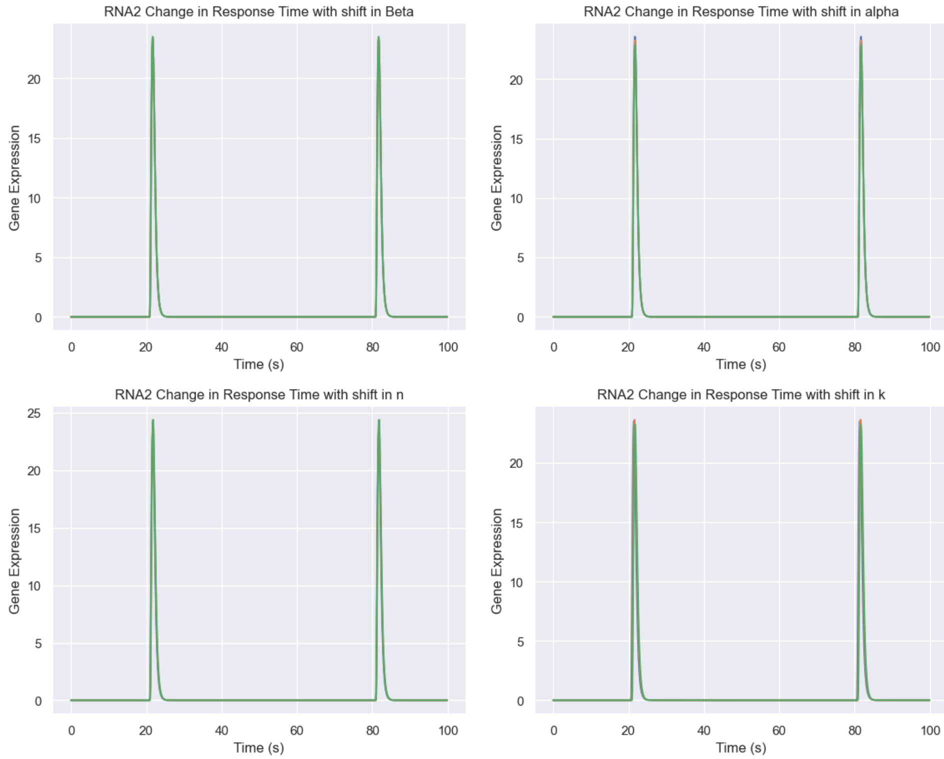

Figure 7: Changing parameters graphs for the Random Network 3 with AND gates

7.4 AND gates–random network 3 equations and graphs

$$\frac{\delta B}{\delta t} = \beta \frac{A^n}{k^n + A^n} \frac{k^n}{k^n + E^n} - \alpha B \tag{41}$$
$$\frac{\delta C}{\delta t} = \beta \frac{D^n}{k^n + D^n} - \alpha C \tag{42}$$
$$\frac{\delta D}{\delta t} = \beta \frac{A^n}{k^n + A^n} - \alpha D \tag{43}$$
$$\frac{\delta E}{\delta t} = \beta \frac{B^n}{k^n + B^n} - \alpha E \tag{44}$$
$$\frac{\delta F}{\delta t} = \beta \frac{D^n}{k^n + D^n} \frac{k^n}{k^n + G^n} - \alpha F \tag{45}$$
$$\frac{\delta G}{\delta t} = \beta \frac{C^n}{k^n + C^n} - \alpha G \tag{46}$$
$$\frac{\delta H}{\delta t} = \beta \frac{I^n}{k^n + I^n} - \alpha H \tag{47}$$
$$\frac{\delta I}{\delta t} = \beta \frac{J^n}{k^n + J^n} \frac{k^n}{k^n + H^n} - \alpha I \tag{48}$$
$$\frac{\delta J}{\delta t} = \beta \frac{E^n}{k^n + E^n} \frac{F^n}{k^n + F^n} - \alpha J \tag{49}$$
$$\frac{\delta K}{\delta t} = \beta \frac{L^n}{k^n + L^n} \frac{k^n}{k^n + M^n} - \alpha K \tag{50}$$
$$\frac{\delta L}{\delta t} = \beta \frac{J^n}{k^n + J^n} - \alpha L \tag{51}$$
$$\frac{\delta M}{\delta t} = \beta \frac{L^n}{k^n + L^n} \frac{K^n}{k^n + K^n} - \alpha M \tag{52}$$
$$\frac{\delta N}{\delta t} = \beta \frac{H^n}{k^n + H^n} \frac{M^n}{k^n + M^n} - \alpha N \tag{53}$$

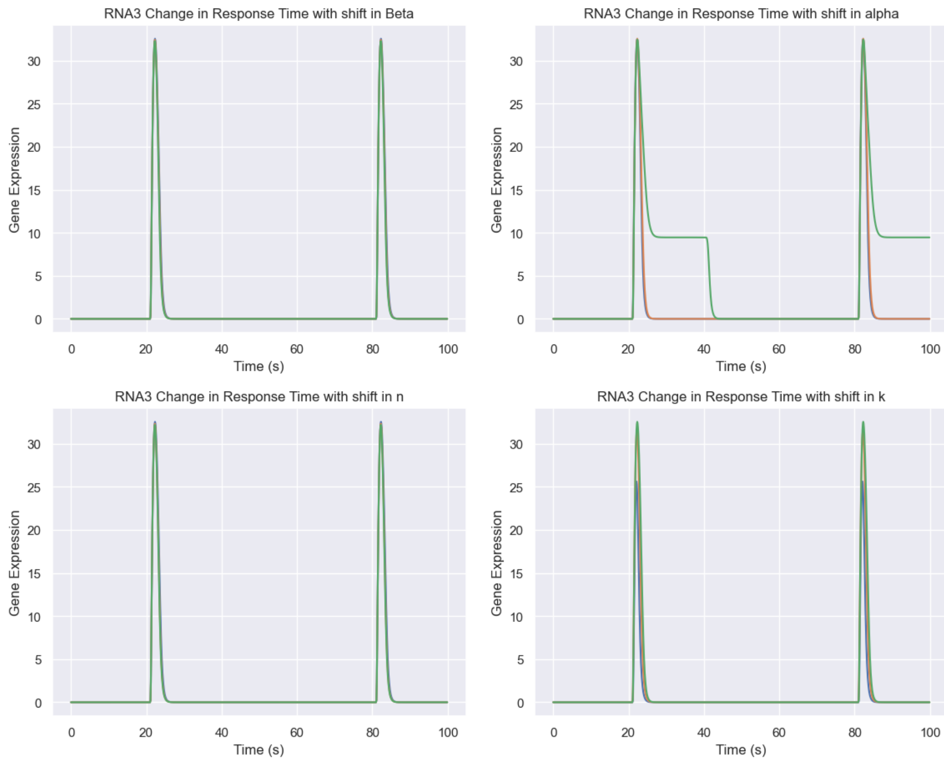

Figure 8: Changing parameters graphs for the Random Network 3 with AND gates

7.5 OR gates–modular network equations and graphs

$$\frac{\delta B}{\delta t} = \beta \frac{A^n}{k^n + A^n} - \alpha B \tag{54}$$

$$\frac{\delta C}{\delta t} = \beta \frac{B^n}{k^n + B^n} - \alpha C \tag{55}$$

$$\frac{\delta D}{\delta t} = \beta \frac{B^n + k^n + B^n k^n}{(k^n + C^n)(k^n + B^n)} - \alpha D \tag{56}$$

$$\frac{\delta E}{\delta t} = \beta \frac{A^n}{k^n + A^n} - \alpha E \tag{57}$$

$$\frac{\delta F}{\delta t} = \beta \frac{E^n}{k^n + E^n} - \alpha F \tag{58}$$

$$\frac{\delta G}{\delta t} = \beta \frac{E^n + k^n + E^n k^n}{(k^n + F^n)(k^n + E^n)} - \alpha G \tag{59}$$

$$\frac{\delta H}{\delta t} = \beta \frac{D^n + G^n + D^n G^n}{(k^n + G^n)(k^n + D^n)} - \alpha H \tag{60}$$

$$\frac{\delta K}{\delta t} = \beta \frac{D^n + G^n + D^n G^n}{(k^n + G^n)(k^n + D^n)} - \alpha K \tag{61}$$

$$\frac{\delta I}{\delta t} = \beta \frac{H^n}{k^n + H^n} - \alpha I \tag{62}$$

$$\frac{\delta J}{\delta t} = \beta \frac{H^n + k^n + H^n k^n}{(k^n + K^n)(k^n + H^n)} - \alpha J \tag{63}$$

$$\frac{\delta L}{\delta t} = \beta \frac{K^n}{k^n + K^n} - \alpha L \tag{64}$$

$$\frac{\delta M}{\delta t} = \beta \frac{K^n + k^n + K^n k^n}{(k^n + L^n)(k^n + K^n)} - \alpha M \tag{65}$$

$$\frac{\delta N}{\delta t} = \beta \frac{J^n + M^n + J^n M^n}{(k^n + M^n)(k^n + J^n)} - \alpha N \tag{66}$$

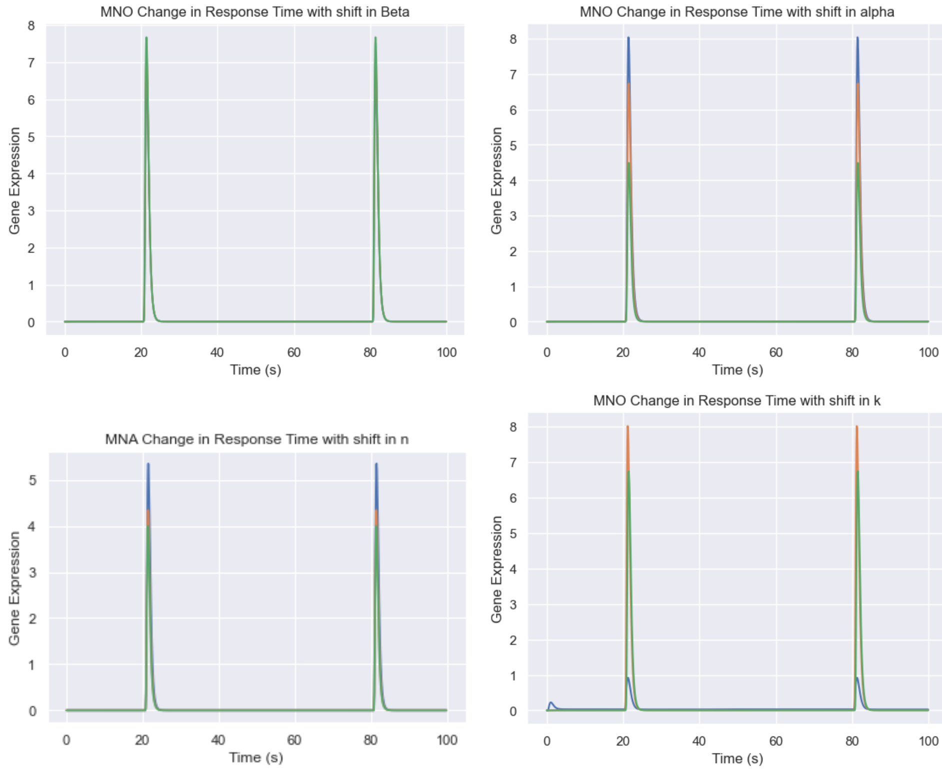

Figure 9: Changing parameters graphs for the Modular Network with OR gates

7.6 OR gates–random network 1 equations and graphs

$$\frac{\delta B}{\delta t} = \beta\frac{C^n + k^n + C^n k^n}{(k^n + C^n)(k^n + D^n)} - \alpha B \tag{67}$$

$$\frac{\delta C}{\delta t} = \beta\frac{I^n}{k^n + I^n} - \alpha C \tag{68}$$

$$\frac{\delta D}{\delta t} = \beta\frac{A^n + 2k^n + 2A^n k^n + K^{2n}}{(k^n + A^n)(k^n + F^n)(k^n + J^n)} - \alpha D \tag{69}$$

$$\frac{\delta E}{\delta t} = \beta\frac{G^n}{k^n + G^n} - \alpha E \tag{70}$$

$$\frac{\delta F}{\delta t} = \beta\frac{G^n}{k^n + G^n} - \alpha F \tag{71}$$

$$\frac{\delta G}{\delta t} = \beta\frac{A^n}{k^n + A^n} - \alpha G \tag{72}$$

$$\frac{\delta H}{\delta t} = \beta\frac{I^n + k^n + I^n k^n}{(k^n + I^n)(k^n + B^n)} - \alpha H \tag{73}$$

$$\frac{\delta I}{\delta t} = \beta\frac{J^n}{k^n + J^n} - \alpha I \tag{74}$$

$$\frac{\delta J}{\delta t} = \beta\frac{L^n}{k^n + L^n} - \alpha J \tag{75}$$

$$\frac{\delta K}{\delta t} = \beta\frac{J^n}{k^n + J^n} - \alpha K \tag{76}$$

$$\frac{\delta L}{\delta t} = \beta\frac{E^n + F^n + E^n F^n}{(k^n + E^n)(k^n + F^n)} - \alpha L \tag{77}$$

$$\frac{\delta M}{\delta t} = \beta\frac{L^n + K^n + L^n K^n}{(k^n + L^n)(k^n + K^n)} - \alpha M \tag{78}$$

$$\frac{\delta N}{\delta t} = \beta\frac{H^n + M^n + H^n M^n}{(k^n + H^n)(k^n + M^n)} - \alpha N \tag{79}$$

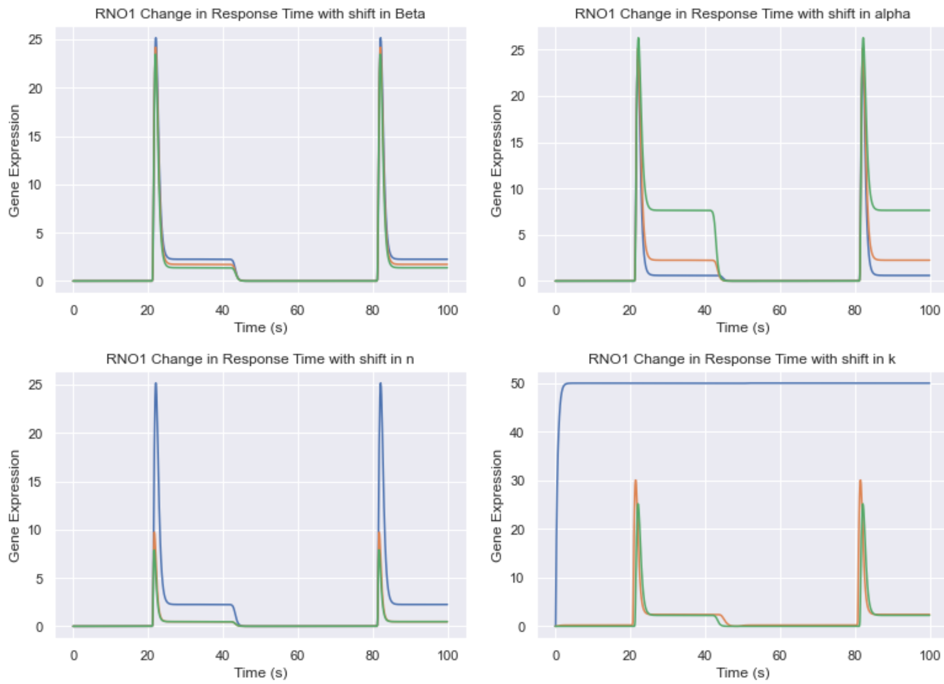

Figure 10: Changing parameters graphs for the Random Network 1 with OR gates

7.7 OR gates–random network 2 equations and graphs

$$\frac{\delta B}{\delta t} = \beta \frac{C^n}{k^n + C^n} - \alpha B \tag{80}$$

$$\frac{\delta C}{\delta t} = \beta \frac{E^n + k^n + E^n k^n}{(k^n + E^n)(k^n + B^n)} - \alpha C \tag{81}$$

$$\frac{\delta D}{\delta t} = \beta \frac{A^n + k^n + A^n k^n}{(k^n + A^n)(k^n + F^n)} - \alpha D \tag{82}$$

$$\frac{\delta E}{\delta t} = \beta \frac{A^n + D^n + A^n D^n}{(k^n + A^n)(k^n + D^n)} - \alpha E \tag{83}$$

$$\frac{\delta F}{\delta t} = \beta \frac{G^n}{k^n + G^n} - \alpha F \tag{84}$$

$$\frac{\delta G}{\delta t} = \beta \frac{D^n}{k^n + D^n} - \alpha G \tag{85}$$

$$\frac{\delta H}{\delta t} = \beta \frac{B^n + k^n + B^n k^n}{(k^n + B^n)(k^n + I^n)} - \alpha H \tag{86}$$

$$\frac{\delta I}{\delta t} = \beta \frac{H^n}{k^n + H^n} - \alpha I \tag{87}$$

$$\frac{\delta J}{\delta t} = \beta \frac{F^n + k^n + F^n k^n}{(k^n + F^n)(k^n + L^n)} - \alpha J \tag{88}$$

$$\frac{\delta K}{\delta t} = \beta \frac{I^n}{k^n + I^n} - \alpha K \tag{89}$$

$$\frac{\delta L}{\delta t} = \beta \frac{K^n}{k^n + K^n} - \alpha L \tag{90}$$

$$\frac{\delta M}{\delta t} = \beta \frac{H^n + k^n + H^n k^n}{(k^n + H^n)(k^n + K^n)} - \alpha M \tag{91}$$

$$\frac{\delta N}{\delta t} = \beta \frac{J^n + M^n + J^n M^n}{(k^n + J^n)(k^n + M^n)} - \alpha N \tag{92}$$

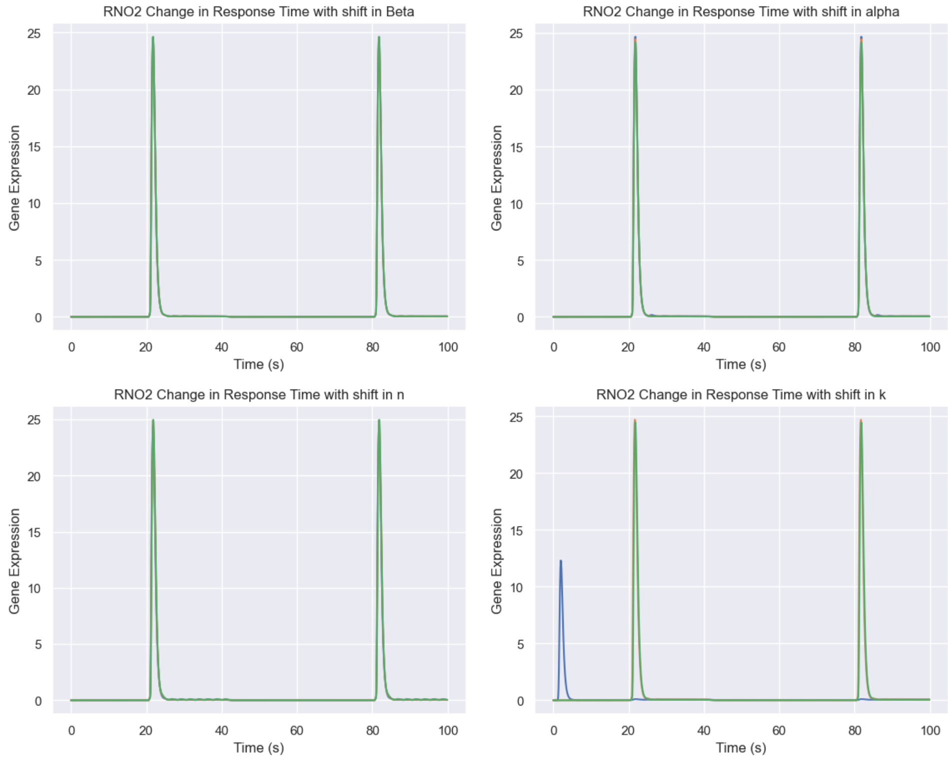

Figure 11: Changing parameters graphs for the Random Network 2 with OR gates

7.8 OR gates–random network 3 equations and graphs

$$\frac{\delta B}{\delta t} = \beta\frac{A^n + k^n * A^n k^n}{(k^n + A^n)(k^n + E^n)} - \alpha B \tag{93}$$

$$\frac{\delta C}{\delta t} = \beta\frac{D^n}{k^n + D^n} - \alpha C \tag{94}$$

$$\frac{\delta D}{\delta t} = \beta\frac{A^n}{k^n + A^n} - \alpha D \tag{95}$$

$$\frac{\delta E}{\delta t} = \beta\frac{B^n}{k^n + B^n} - \alpha E \tag{96}$$

$$\frac{\delta F}{\delta t} = \beta\frac{D^n + k^n + D^n k^n}{(k^n + D^n)(k^n + G^n)} - \alpha F \tag{97}$$

$$\frac{\delta G}{\delta t} = \beta\frac{C^n}{k^n + C^n} - \alpha G \tag{98}$$

$$\frac{\delta H}{\delta t} = \beta\frac{I^n}{k^n + I^n} - \alpha H \tag{99}$$

$$\frac{\delta I}{\delta t} = \beta\frac{J^n + k^n + J^n k^n}{(k^n + J^n)(k^n + H^n)} - \alpha I \tag{100}$$

$$\frac{\delta J}{\delta t} = \beta\frac{E^n + E^n + E^n F^n}{(k^n + E^n)(k^n + F^n)} - \alpha J \tag{101}$$

$$\frac{\delta K}{\delta t} = \beta\frac{L^n + k^n + L^n k^n}{(k^n + L^n)(k^n + M^n)} - \alpha K \tag{102}$$

$$\frac{\delta L}{\delta t} = \beta\frac{J^n}{k^n + J^n} - \alpha L \tag{103}$$

$$\frac{\delta M}{\delta t} = \beta\frac{L^n + K^n + L^n K^n}{(k^n + L^n)(k^n + K^n)} - \alpha M \tag{104}$$

$$\frac{\delta N}{\delta t}\beta\frac{H^n + M^n + H^n M^n}{(k^n + H^n)(k^n + M^n)} - \alpha N \tag{105}$$

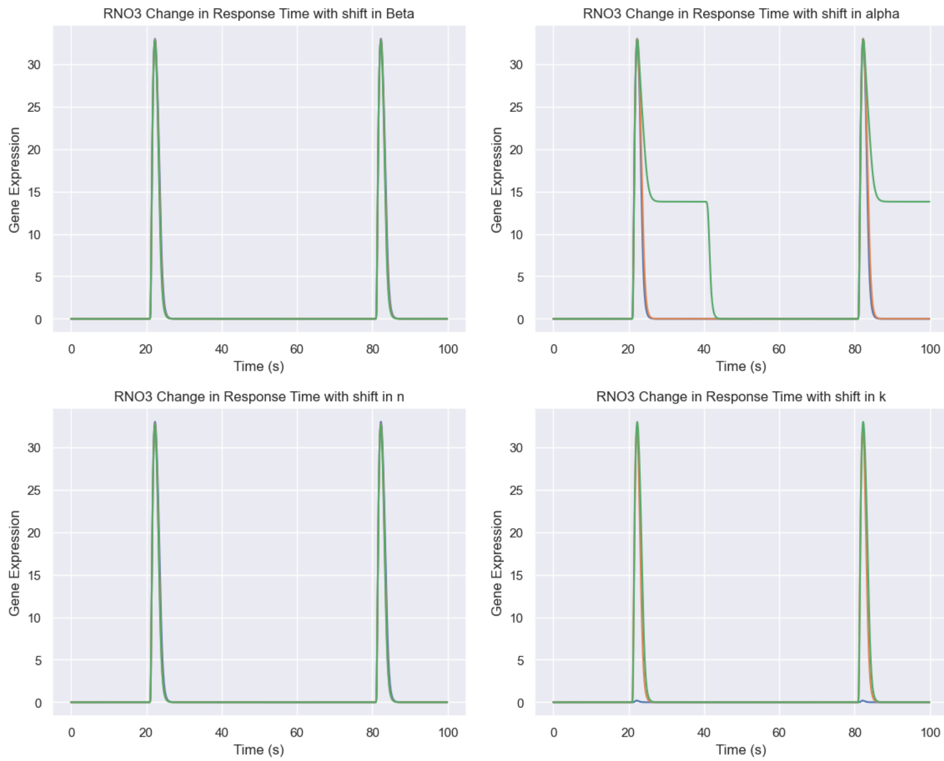

Figure 12: Changing parameters graphs for the Random Network 3 with OR gates

7.9 Tables of Data

Time from Response to Peak	
Network	time (min)
M-and	1.5
R1-and	1.8
R2-and	1.9
R3-and	2.0
M-or	1.5
R1-or	2.1
R2-or	1.8
R3-or	2.0

% Change in β		
Network	1.1x increase	1.2x increase
M-and	11.30	20.15
R1-and	-3.514	-6.740
R2-and	0.575	0.967
R3-and	-0.369	-0.804
M-or	7.994	13.90
R1-or	-3.930	-6.730
R2-or	0.402	0.671
R3-or	-0.324	-0.701

% Change in α		
Network	2x increase	3x increase
M-and	-21.57	-57.39
R1-and	3.625	8.288
R2-and	-1.292	-3.022
R3-and	0.103	-0.221
M-or	-16.212	-44.16
R1-or	5.288	10.01
R2-or	-0.853	-2.09
R3-or	0.024	-0.277

% Change in k		
Network	5x increase	10x increase
M-and	181.06	274.85
R1-and	-32.11	-26.398
R2-and	0.578	-0.984
R3-and	22.697	27.01
M-or	771.56	632.66
R1-or	-39.946	-49.69
R2-or	100.62	98.72
R3-or	15708.6	16185.1

% Change in n		
Network	2x increase	3x increase
M-and	-18.846	-25.321
R1-and	-3.405	-4.03
R2-and	3.80	-4.825
R3-and	-0.664	-1.09
M-or	-16.413	-21.499
R1-or	-61.30	-68.63
R2-or	1.627	2.088
R3-or	-0.721	-1.107

8 References

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3 J. B. Stock and M. D. Baker, "Chemotaxis," ScienceDirect, Jan. 01, 2009.