35th Annual International Conference of the IEEE EMBS
Osaka, Japan, 3 - 7 July, 2013

G-networks Towards Synthetic Biology: A Brief Review

Haseong Kim[1] and Erol Gelenbe[2]

Abstract— **G-networks and the Random Neural Network are a class of stochastic models that have a broad range applications ranging from modeling neuronal ensembles, gene regulatory networks, and the performance of computer systems and networks and modeling of energy flows in systems with renewable energy sources. Eaarlier applications include learning, bio-medical image processing, and network routing. Gene regulatory networks (GRNs) consist of thousands of genes and proteins which dynamically interact with each other. Once these regulatory structures are revealed, one must understand their dynamical behaviors through pathway activities. GRN dynamics are often investigated via stochastic models since molecular interactions are discrete and stochastic. However, this stochastic nature requires substantial computation to find the steady-state solution of the GRNs where thousands of genes are involved. This review focuses on a stochastic GRN modeling techniques based on G-networks which provide the analytical steady-state solution for efficient GRN dynamics. Three applications of G-networks to GRNs show that this novel approach serves to detect abnormalities from gene expression data, and that they help to explicit the behavior of complicated GRN models by dividing the gene regulatory processes into DNA and protein layers. Appropriate reverse engineering methods similar to neural network learning allows the G-network to provide important insight into the manner in which GRNs respond to external conditions, offering biologically meaningful and clinically useful information, and as an exploratory design tool for synthetic biology.**

Index Terms— **-Networks, Gene Regulatory Networks, Stochastic Modeling, Synthetic Biology-Networks, Gene Regulatory Networks, Stochastic Modeling, Synthetic BiologyG**

I. Introduction

G-networks [18] and the Random Neural Network [17], [41] are a class of stochastic models inspired from queueing network theory [38]. They have a broad range of applications ranging from the modeling of neuronal ensembles [14], [?], task optimisation in computer systems and decision environments [1], [42], [43], energy optimisation in packet networks [39], [37], network admission control [27], modeling of energy flows in systems with renewable energy sources [33], [32], learning [36], [34], image and video processing [3], [13], [40], [15], detection of explosive mines [23], [25], network routing [54], network security [28], [35], the analysis of chemical reactions [30] and all the way to the modeling of gene regulatory networks. Thus these probability models are a link between operations research and computer system performance on the one hand, and fundamental subjects in system biology including the neuroscience and genetics on the other.

Gene regulatory networks (GRNs) play a key role to uncover the functions of genes and their genetic effect on a specific phenotype. Thanks to the advancement of measuring technology such as microarrays, biologists easily capture the expression patterns of mRNA/protein under different conditions. Along with these bursts of biological data, various statistical/mathematical models have been introduced for investigating the dynamic behaviors of a system. These dynamics can be defined as quantitative changes of gene expression level responding to the environmental conditions of the system, which provides important clues connecting the gene behaviors to a specific phenotype. Due to the stochastic nature of biomolecular reactions, the GRN models have been widely described by stochastic processes which could be more significant at a single molecule level [58], and stochastic simulation techniques are commonly used in this area to provide a solution to a set of biomolecular reactions [45].

However, simulating every single reaction in a large-scale GRN gives rise to heavy computation times so that far more efficient stochastic modeling techniques are required. In [22], a new approach to the steady-state analysis of GRNs based on G-Network theory [20], [21] was introduced while G-networks were firstly applied to GRNs with simplifying assumptions concerning gene expression in [2]. Other papers regarding the theory of G-networks with positive and negative customers, signals, triggers, and resets can be found in [20], [21], [26], [24]. Specifically, the use of negative customers enables us to model negative gene regulatory interactions, and G-networks provide a closed form solution in steady-state, which enables us to extend the analysis to the dynamics of large-scale GRNs.

However, the G-network approach in GRN modeling still has some difficulties caused by the large number of parameters. In this review, we will revisit the G-network theory and its application for abnormal pathway detection [51], [50] where the abnormality is defined as an unexpected different activation level of a pathway given a normal condition. The rational of this application is to map gene regulation processes to the reactions of the G-network model and then to reduce the number of model parameters on the basis of appropriate biological assumptions.

II. Gene Regulatory Principles

Gene regulation is involved with the activities of various mRNA and protein molecules such as transcription factors, repressors, and activators (Fig. 1). Depending on cell growth conditions, there are several copies of partially replicated chromosomes [58]. Each copy of the genes spontaneously switches ON and OFF at given rates. In ON state, an mRNA is synthesized from the DNA template by RNA polymerases, called transcription which is followed by translation. In translation of a prokaryote, multiple ribosomes spaced in about 80 nucleotides [57] bind successively to the mRNA as soon as it is accessible to the mRNA strand and corresponding proteins are produced from the attached ribosomes. These translation processes are continued until the mRNA is degraded by an RNAse-E. Many studies have interpreted the variation of the protein levels in terms of protein bursting which takes place in short periods of high expression intensity followed by long periods of low expression [63], [11]. In addition, there are various molecules that are involved in post-translation processes such as protein multimerization and phosporylation. Also DNA binding

[1]H. Kim is with Faculty of Systems and Synthetic Biology Center, Korea Research Institute of Bioscience and Biotechnology, South Korea haseong at kribb.re.kr

[2]E. Gelenbe is with Professor of Department of Electrical and Electronic Engineering, Imperial College, London, SW7 2BT, UK e.gelenbe at imperial.ac.uk

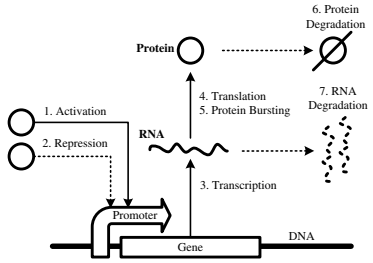

Fig. 1. Seven biological processes for gene expression.

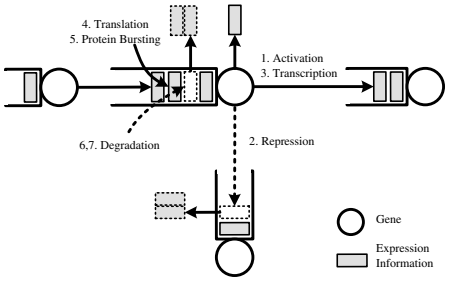

Fig. 2. Seven biological processes for gene expression in a G-network model.

proteins, especially activators and repressors, can regulate their target gene expressions by increasing and decreasing the binding affinity between the target DNA and RNA polymerases. Lastly, degradation of mRNAs and proteins is one of the main factors for the tight control of gene expressions in a cell. An mRNA is cleaved by RNase-E and then is degraded by a combination of ribonucleases including $3' - 5'$ exonucleases, while proteins can be degraded by ubiquitination or protease activity.

A. G-networks for GRNs

As discussed above, gene expression is considered as a set of interactions of discrete molecules; hence stochastic modeling is a natural way to describe these processes. In this paper, a model is defined as a set of mathematical equations to describe various biochemical reactions for gene regulation principles. Typically, the solution of this stochastic model is found using the Gillespie algorithm [44], [53] which is a broadly applicable numerical method for such stochastic models. However, the purely numerical approach to the reaction equations limits its applicability to large-scale stochastic model. As mentioned in the Introduction, G-networks have an analytic steady-state solution for a stochastic model even if it consists of a large number of reaction equations.

G-network theory was firstly applied to GRNs with simplifying assumptions concerning gene expression in [2] and a more generalized model for GRNs was introduced in [22]. In terms of GRNs, a node in the G-network is a "place" where "customers" are stored, and a customer is a latent variable containing gene expression information. We will follow the idea and notations of G-network modeling in [22]. Let $X_i(t)$ be an integer-valued random variable which represents the lever or intensity expression of the ith gene at time t. If the $X_i(t)$ is zero, the gene i cannot interact with other genes. If the ith gene (placed center in Fig. 2) interacts with other genes, the following events occur:

- **With a rate constant λ_i^+ (λ_i^-), a positive (negative) customer arrives to the ith gene from the external of the system. Translation and protein bursting processes in Figure 2 are for the positive case and degradation process can be represented by the negative customer activity.**
- **With probability p_{ij}^+, gene i activates gene j; when this happens, $X_i(t)$ is depleted by 1 and $X_j(t)$ is increased by 1. Activation and Transcription processes in Figure 2 belong to this case.**
- **With probability p_{ij}^-, gene i inhibits gene j; when this happens, both $X_i(t)$ and $X_j(t)$ are depleted by 1. Repression process in Figure 2.**
- **With probability p_{ijl} gene i joins with gene j to act upon gene l in excitatory mode, as a result of which both $X_i(t)$ and $X_j(t)$ are reduced by 1, while $X_l(t)$ is increased by 1. However, our models, in this study, do not include this type of interaction.**
- **With probability d_i, which is defined as follows,**

$$d_i + \sum_{j=1}^{n} \left(p_{ij}^+ + p_{ij}^- + \sum_{l=1}^{n} p_{ijl} \right) = 1$$

the signal of gene i exits the system so $X_i(t)$ is depleted by 1.

The network state is represented by the n-vector of non-negative integers $\mathbf{x} = \{x_1, ..., x_n\}$, and we also define the vectors of non-negative integers $\mathbf{x}_i^+ = \{x_1, ..., x_i+1, ..., x_n\}$, $\mathbf{x}_i^- = \{x_1, ..., x_i-1, ..., x_n\}$, $\mathbf{x}_{ij}^{+-} = \{x_1, ..., x_i+1, x_j-1, ..., x_n\}$, Now let the random process $\mathbf{X}(t) = \{X_1(t), ..., X_n(t)\}$ be defined with $X_i(t)$. If $P(\mathbf{x}, t)$ is the probability that $\mathbf{X}(t)$ takes the value $\mathbf{x}$ at time t, then the balanced equation of the G-networks is:

$$\begin{aligned} P(\mathbf{x}, t+\Delta t) = \sum_{i=1}^{n} \Big[& (\lambda_i^+ \Delta t + o(\Delta t)) P(\mathbf{x}_i^-, t) I(\mathbf{x}_i > 0) \\ & + (\lambda_i^- \Delta t + o(\Delta t)) P(\mathbf{x}_i^+, t) \\ & + \sum_{j=1}^{n} \Big\{ (\mu_i p_{ij}^+ \Delta t + o(\Delta)) P(\mathbf{x}_{ij}^{+-}, t) I(\mathbf{x}_j > 0) \\ & + (\mu_i p_{ij}^- \Delta t + o(\Delta)) P(\mathbf{x}_{ij}^{++}, t) \\ & + (\mu_i p_{ij}^- \Delta t + o(\Delta)) P(\mathbf{x}_i^+, t) I(\mathbf{x}_j = 0) \Big\} \\ & + (\mu_i d_i \Delta t + o(\Delta t)) P(\mathbf{x}_i^+, t) \\ & + (1 - (\lambda_i^+ + \lambda_i^- + \mu_i) \Delta t + o(\Delta t)) P(\mathbf{x}, t) \Big] \end{aligned} \tag{1}$$

where μ_i is the activity rate of the ith gene, and the quantity $I(C)$ is 1 if C is true and 0 otherwise. Throughout, the quantity $o(\Delta t) \to 0$ as $\Delta t \to 0$. The first term in the above equations describes the increment of the ith genes activation level by an effect that is external to the network, while the second term describes the decrement of the ith gene expression level by an external negative or inhibitory effect. The third term is the probability that the ith gene affects the j positively so as to reinforce its expression. The fourth and fifth terms describe a negative effect from the ith gene to decrease the jth gene's expression. The sixth term describe the transition that occurs when is the ith gene's expresion level is autonomously depleted, and the last term describes the situation where no transitions occur in time δt.

From these equations it has been shown [22] that the steady-state probability that gene i is expressed is given by:

$$\begin{aligned} q_i &= \frac{\Lambda_i^+}{\mu_i + \Lambda_i^-} \\ \text{where} \quad \Lambda_i^+ &= \lambda_i^+ + \sum_{j=1}^{n} q_j \mu_j p_{ji}^+ \\ \Lambda_i^- &= \lambda_i^- + \sum_{j=1}^{n} q_j \mu_j p_{ji}^- \end{aligned} \tag{2}$$

Furthermore the following product form solution satisfies ((1)) in steady-state [21].

$$P(\mathbf{X}=\mathbf{x})=\prod_{i=1}^{n} q_i^{x_i}(1-q_i) \tag{3}$$

when the $q_i < 1$. That is, by substituting ((2)) and ((3)) into ((1)), then ((1)) is satisfied [21].

III. Abnormal Pathway Detection

Among several applications for G-networks [51], [50], [52], we will describe how to detect abnormal pathways [50] in GRNs. Differentially Expressed Gene (DEG) analyses are commonly used with case-control gene expression data. But they are limited in detecting defective pathways since they only observe the amount of expression of a gene itself rather than considering the flows of expression signals. So, we focused on estimating the transition probabilities (p_{ji}^{+}, p_{ji}^{-}) which indicate the information flow and we compare them to their initial assumed values to identify the abnormal pathway activities between two different conditions such as normal and disease.

We assume that the number of customers or activation levels for the different genes is proportional to the mRNA expression levels which were observed in a steady-state. If we denote the *average mRNA level* of the ith gene by $\bar{x}_i$, then from the product form solution we know that $\bar{x}_i = q_i/(1-q_i)$ in ((3)). Therefore the steady-state probability that there is at least one mRNA of the ith gene is

$$q_i = \frac{\bar{x}_i}{\bar{x}_i + 1} \tag{4}$$

The main goal of this approach is to identify transition probabilities, p_{ji}^{+} and p_{ji}^{-} in ((2)), that a customer moves from the jth gene to the ith gene in an abnormal condition, and compare them with the corresponding initial transition probabilities.

1) Abnormal Pathway Detection Algorithm: Let λ_i^{+} and λ_i^{-} be the positive and negative customer input rates, respectively, and μ_i be the service rate. First, we determined these parameter values in a normal condition with the following assumptions:

- Let the transition probabilities be $\mathbf{p}_j = \{p_{ji}^{+}, p_{ji}^{-}\}$ and $\mathbf{p}_j$ have uniform probabilities. That is all elements in $\mathbf{p}_j$ have $1/(D_j^{out}+1)$ where D_j^{out} is the out-degree of gene j
- The positive customer input rate, λ_i^{+}, can be set as $\lambda_i^{+} = D_i^{in}$ where D_i^{in} is the in-degree.
- The firing rate, μ_i, is proportional to the out-degree distribution of the ith gene; $\mu_i = D_i^{out}$+1 where the additional one is for the case that a customer goes out of the system.

Then, the only parameter we do not know is λ_i^{-} which can be easily obtained by optimizing the follow objective function.

$$q_i - f_i(\lambda_i^{+}, \mu_i, \mathbf{q}_j, \mathbf{p}_j; \lambda_i^{-}) \tag{5}$$

Now, let $\mathbf{p}_j'$ be the transition probability in an abnormal condition. Our interest is to estimate this $\mathbf{p}_j'$ given all the other parameters are the same with that of the normal condition. So it is obvious that $\mathbf{p}_j' = \mathbf{p}_j$ if the abnormal data is the same as the normal data. Let q_i' be the observed steady-state probability of the ith gene in the abnormal condition. We find the probabilities by minimizing the following sum of squared error with a constraint $0 \le \mathbf{p}_j' \le 1$:

$$\sum_i (q_i' - f_i(\mathbf{q}_j', \lambda_i^{+}, \lambda_i^{-}, \boldsymbol{\mu}_{ij}; \mathbf{p}_j'))^2 \tag{6}$$

In all the optimization steps to minimize ((6)), we use the Barzilai-Borwein spectral method in the BB package [65] which is closely related to the well known Conjugate-Gradient method. However this approach yields local minima so we need following iterative search:

1) Set the solution boundary, $[B_{lower}, B_{upper}]$, of the $\mathbf{p}_j'$ as 0 and $2 \times \mathbf{p}_j$, respectively
2) Find total H solutions $\{\mathbf{p}_j'^{(1)}, \ \dots \ , \mathbf{p}_j'^{(H)}\}$ with initial probability values which are randomly selected from $[B_{lower}, B_{upper}]$ ($H = 2000$).
3) Reset the boundary by truncating the lower and upper 5% of the estimated solutions.
4) Go to the 2nd step and repeat this iteration until the standard deviation of $\{\mathbf{p}_j'^{(1)}, \ \dots \ , \mathbf{p}_j'^{(H)}\}$ is less than 0.01
5) $\hat{\mathbf{p}}_j' = \sum_{i=1}^{H} \{\mathbf{p}_j'^{(1)}, \ \dots \ , \mathbf{p}_j'^{(H)}\}$

As the last step of this algorithm, we tested the significant of the estimated $\hat{p}_{ij}'$ by permuting the samples across the normal and abnormal group to generate a null distribution. The null hypothesis of this test is $\hat{p}_{ji}' \neq p_{ji}$. To precede the test, its samples were shuffled at random and divided into normal and abnormal groups with the same sizes of the original groups. Then obtain the transition probability, $p_{ij}^{(m)}$, of the mth permutation by performing the same algorithm with the permutated data. Let M be the number of permutations then the empirical p-value of $\hat{p}_{ij}'$ can be obtained as follows,

$$p\text{-value of } \hat{p}_{ij}' = \begin{cases} \frac{1}{M}\sum_{m=1}^{M} I(\hat{p}_{ij}' \le p_{ij}^{(m)}) & \text{if } p_{ij}' > p_{ij} \\ \frac{1}{M}\sum_{m=1}^{M} I(\hat{p}_{ij}' \ge p_{ij}^{(m)}) & \text{if } p_{ij}' < p_{ij} \end{cases}$$

where $I(C)$ is the indicator function. Thus if the p-value is less than a criterion α then the null hypothesis is rejected. We used $\alpha = 0.001$.

2) Brain Tumour with p53 Networks: In order to assess our approach using real experimental data, we built a p53 network which is a well studied system in human cells and whose most important feature is tumor suppression when DNA is damaged. The regulatory structure of the p53 pathway with 28 genes was constructed on the basis of the KEGG database [49], and we collected a microarray mRNA expression dataset (GSE12941) from GEO [4]. This dataset consists of 10 non-tumor liver tissue and 10 hepatocellular carcinoma (HCC) samples. Before applying the proposed method, the data were normalized and scaled with mean 3 and variance 1 because the average number of mRNAs of a gene in a single cell is assumed to be approximately 3 (The mRNA transcription and degradation rates are assumed to be $0.0062sec^{-1}$ and $0.002sec^{-1}$ from [63] so that the average is $0.0062/0.002 \approx 3$).

In Figure 3, we can simply draw following two conclusions. First, ATM/ATR-CHEK1/CHEK2 pathways are well known to be activated when the DNA is damaged [8]. Despite the apparent lack of significance of ATM and ATR in their t-tests, their positive pathways are shown to be significantly inactivated in cancer samples. Also the negative pathways between MDM4-MDM2 and p53 are significantly activated. So these results indicate that p53 seems to stay at low levels in cancer samples, which means its function of tumor suppression is not activated in tumor cells. The other conclusion is that caspase (CASP3, CASP8, and CASP9) mediated pathways which are well known to trigger cell apoptosis are not activated or significantly inactivated in tumor samples. The p-values are also not significant in the t-test. These results seem to show that our method properly reflects the properties of the tumor samples.

IV. Discussion

Thanks to the development of measurement devices and technology in biology, a vast amount of biological data is being generated every day, and pushes researchers toward the genome wide view of a system and appropriate tools which can handle the large amount of data are required. In this

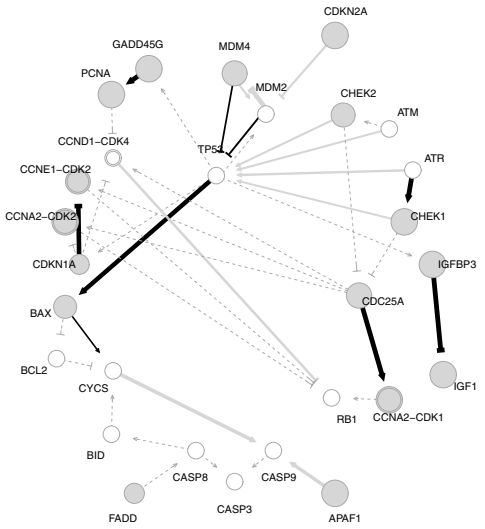

Fig. 3. The p53 network with the results of GSE12941 dataset analysis. The solid line represents significantly activated (black) or inactivated (grey) pathways while the dashed line indicates non-significant pathways. Wider lines represent more significant pathways. The grey nodes are the significant DEGs from the t-test. The radius of a node is larger if its DEG test is more significant with a 0.05 significant level. White nodes indicate non-significant genes.

review, we have shown how G-network theory that arises from neural network and queueing network developments, can be used to model GRNs efficiently. Since the nature of gene regulation processes is discrete and probabilistic, stochastic modeling is an appropriate choice for describing biological systems. However, the usage of conventional probabilistic modeling approaches with the Gillespie algorithm is limited by their computational difficulty especially when the number of molecules is large. This computational cost due to large memory space and non-polynomial computational complexity are basic limitations in conventional stochastic modeling approaches. The G-network modeling approach allows us to obtain the steady-state behaviour of GRNs with only polynomial computational complexity thanks to the product form solution of G-Networks.

However, the approach using G-networks, applied to detecting abnormalities from gene expression data, must be assessed with respect to structural robustness. For example, if an edge is removed or added to the p53 network, would this be readily detected? Once this structural robustness analysis has been carried out, sensitivity analysis of the parameters or genes can help identify the key molecules that are responsible for the phenotype. Also, a living cell exhibits oscillatory behaviors which play an important role in cellular processes such as the circadian clock and the cell cycle. G-network theory currently focuses on the steady-state, though the G-network system equations are time-dependent and can in principle be applied to the oscillatory expressions of a system. However, once a large-scale system is analyzed using G-networks, then it could be narrowed down into small network modules and their detailed dynamics can be addressed by conventional techniques such as the Gillespie algorithm. Also an analytical study for finding the solution of the transients, such as a quasi-stable systems, can be addressed using approaches such as [62].

Another interesting extension would be to study bioengineered organisms in synthetic biology to "engineer living systems" with promising applications to health, energy and environmental problems. Though synthetic biology requires expertise from diverse disciplines, modeling is becoming important for designing new complex synthetic systems [64], [66]. Here again, G-network modeling could be useful. Again, determining how a synthetically introduced biological circuit will affect the behavior of a cell through its generations via conventional stochastic modeling is difficult due to the complexity and very large-scale of a living system. G-Networks which predict long-run behavior could be used to reveal the behavioral and evolutionary properties of the synthetic system, and to determine whether in the long run a complex synthetic biological system attains a safe state. Such assessment and monitoring methods could be essential for the safe development of synthetic biology.

REFERENCES

[1] J. Aguilar and E. Gelenbe, "Task assignment and transaction clustering heuristics for distributed systems," *Information Sciences*, vol. 97, no. 1, pp. 199–219, 1997.

[2] A. Arazi, E. Ben-Jacob, and U. Yechiali, "Bridging genetic networks and queueing theory," *Physica A: Statistical Mechanics and its Applications*, vol. 332, pp. 585–616, 2004.

[3] V. Atalay and E. Gelenbe, "Parallel algorithm for colour texture generation using the random neural network model," *International Journal of Pattern Recognition and Artificial Intelligence*, vol. 6, no. 2-3, pp. 437–446, 1992.

[4] T. Barrett, D. Troup, S. Wilhite, P. Ledoux, D. Rudnev, C. Evangelista, I. Kim, A. Soboleva, M. Tomashevsky, and R. Edgar, "NCBI GEO: mining tens of millions of expression profiles–database and tools update," *Nucleic acids research*, vol. 35, no. Database issue, p. D760, 2007.

[5] J. Bower and H. Bolouri, *Computational modeling of genetic and biochemical networks*. The MIT Press, 2004.

[6] D. Bratsun, D. Volfson, L. Tsimring, and J. Hasty, "Delay-induced stochastic oscillations in gene regulation," *Proceedings of the National Academy of Sciences*, vol. 102, no. 41, p. 14593, 2005.

[7] ——, "Delay-induced stochastic oscillations in gene regulation," *Proceedings of the National Academy of Sciences*, vol. 102, no. 41, pp. 14 593–14 598, 2005.

[8] C. Brown, S. Lain, C. Verma, A. Fersht, and D. Lane, "Awakening guardian angels: drugging the p53 pathway," *Nature Reviews Cancer*, vol. 9, no. 12, pp. 862–873, 2009.

[9] N. Buchler, U. Gerland, and T. Hwa, "Nonlinear protein degradation and the function of genetic circuits," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 27, p. 9559, 2005.

[10] ——, "Nonlinear protein degradation and the function of genetic circuits," *Proceedings of the National Academy of Sciences*, vol. 102, no. 27, pp. 9559–9564, 2005.

[11] L. Cai, N. Friedman, and X. Xie, "Stochastic protein expression in individual cells at the single molecule level," *Nature*, vol. 440, no. 7082, pp. 358–362, 2006.

[12] I. Cantone, L. Marucci, F. Iorio, M. Ricci, V. Belcastro, M. Bansal, S. Santini, M. Di Bernardo, D. Di Bernardo, and M. Cosma, "A yeast synthetic network for in vivo assessment of reverse-engineering and modeling approaches," *Cell*, vol. 137, no. 1, pp. 172–181, 2009.

[13] C. Cramer and E. Gelenbe, "Video quality and traffic qos in learning-based subsampled and receiver-interpolated video sequences," *IEEE Journal on Selected Areas in Communications*, vol. 18, no. 2, pp. 150–167, 2000.

[14] ——, "Oscillatory corticothalamic response to somatosensory input," *Biosystems*, vol. 48, no. 1, pp. 67–75, 1998.

[15] K. H. E. Gelenbe and V. Kaptan, "Simulating autonomous agents in augmented reality," *Journal of Systems and Software*, vol. 74, no. 3, pp. 255–268, 2005.

[16] M. Elowitz, S. Leibler, *et al.*, "A synthetic oscillatory network of transcriptional regulators," *Nature*, vol. 403, no. 6767, pp. 335–338, 2000.

[17] J.-M. Fourneau and E. Gelenbe, "Random neural networks with multiple classes of signals," *Neural Computation*, vol. 11, no. 4, pp. 953–963, 1999.

[18] ——, "Flow equivalence and stochastic equivalence in g-networks," *Computational Management Science*, vol. 1, no. 2, pp. 179–192, 2004.

[19] T. Gardner, C. Cantor, and J. Collins, "Construction of a genetic toggle switch inEscherichia coli," *Nature*, vol. 403, pp. 339–342, 2000.

[20] E. Gelenbe, "Product-form queueing networks with negative and positive customers," *Journal of Applied Probability*, pp. 656–663, 1991.

[21] ——, "G-networks with triggered customer movement," *Journal of Applied Probability*, pp. 742–748, 1993.

[22] ——, "Steady-state solution of probabilistic gene regulatory networks," *Phys Rev E*, vol. E 76, p. 031903, 2007.

[23] E. Gelenbe and Y. Cao, "Autonomous search for mines," *European Journal of Operational Research*, vol. 108, no. 2, pp. 319–333, 1998.

[24] E. Gelenbe and J. Fourneau, "G-networks with resets," *Performance Evaluation*, vol. 49, no. 1-4, pp. 179–191, 2002.

[25] E. Gelenbe and T. Koçak, "Area-based results for mine detection," *IEEE Trans. on Geoscience and Remote Sensing*, vol. 38, no. 1, pp. 12–24, 2000.

[26] E. Gelenbe and A. Labed, "G-networks with multiple classes of signals and positive customers," *European journal of operational research*, vol. 108, no. 2, pp. 293–305, 1998.

[27] E. Gelenbe, G. Sakellari, and M. D' Arienzo, "Admission of QoS Aware Users in a Smart Network," *ACM Transactions on Autonomous and Adaptive Systems*, vol. 3, no. 1, pp. 4:1–4:28, March 2008.

[28] E. Gelenbe, "Dealing with software viruses: a biological paradigm," *Information security technical reports*, vol. 12, no. 4, pp. 242–250, 2007.

[29] ——, "Steady-state solution of probabilistic gene regulatory networks," *Physical Review*, vol. E 76, no. 3, p. 031903, 2007.

[30] ——, "Network of interacting synthetic molecules in steady state," *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Science*, vol. 464, no. 2096, pp. 2219–2228, 2008.

[31] ——, "Steps towards self-aware networks," *Communications ACM*, vol. 52, no. 7, pp. 66–75, July 2009.

[32] ——, "Energy packet networks: adaptive energy management for the cloud," in *Proceedings CloudCP '12, 2nd International Workshop on Cloud Computing Platforms*. ACM, 2012, p. Article No. 1.

[33] ——, "Energy packet networks: Ict based energy allocation and storage," in *Green Communications and Networking*, vol. 51. Lecture Notes of the Institute for Computer Sciences, Social Informatics and Telecommunications Engineering, 2012, pp. 186–195.

[34] E. Gelenbe and K. F. Hussain, "Learning in the multiple class random neural network," *IEEE Transactions on Neural Networks*, vol. 13, no. 6, pp. 1257–1267, 2002.

[35] E. Gelenbe and G. Loukas, "A self-aware approach to denial of service defence," *Computer Networks*, vol. 51, no. 5, pp. 1299–1314, 2007.

[36] E. Gelenbe, Z.-H. Mao, and Y.-D. Li, "Function approximation with spiked random networks," *IEEE Transactions on Neural Networks*, vol. 10, no. 1, pp. 3–9, 1999.

[37] E. Gelenbe and C. Morfopoulou, "A framewok for energy aware routing in packet networks," *The Computer Journal*, vol. 54, no. 6, 2011.

[38] E. Gelenbe and R. R. Muntz, "Probabilistic models of computer systems: Part i (exact results)," *Acta Informatica*, vol. 7, no. 1, pp. 35–60, 1976.

[39] E. Gelenbe and S. Silvestri, "Reducing power consumption in wired networks," in *24th International Symposium on Computer and Information Sciences (ISCIS '09)*. IEEE, September 2009, pp. 292–297.

[40] E. Gelenbe, M. Sungur, C. Cramer, and P. Gelenbe, "Traffic and video quality with adaptive neural compression," *Multimedia Systems*, vol. 4, no. 6, pp. 357–369, 1996.

[41] E. Gelenbe and S. Timotheou, "Random neural networks with synchronized interactions," *Neural Computation*, vol. 20, no. 9, pp. 2308–2324, 2008.

[42] E. Gelenbe, S. Timotheou, and D. Nicholson, "Fast distributed near-optimum assignment of assets to tasks," *The Computer Journal*, vol. 53, no. 9, pp. 1360–1369, 2010.

[43] E. Gelenbe, S. Timotheou, and D. Nicholson, "Random neural network for emergency management," in *MSAHS*, 2010.

[44] D. Gillespie, "Stochastic simulation of chemical kinetics," *Annu. Rev. Phys. Chem.*, vol. 58, pp. 35–55, 2007.

[45] D. Gillespie *et al.*, "Exact stochastic simulation of coupled chemical reactions," *The journal of physical chemistry*, vol. 81, no. 25, pp. 2340–2361, 1977.

[46] D. Goeddel, D. Yansura, and M. Caruthers, "Binding of synthetic lactose operator DNAs to lactose repressors," *Proceedings of the National Academy of Sciences*, vol. 74, no. 8, pp. 3292–3296, 1977.

[47] I. Golding, J. Paulsson, S. Zawilski, and E. Cox, "Real-time kinetics of gene activity in individual bacteria," *Cell*, vol. 123, no. 6, pp. 1025–1036, 2005.

[48] ——, "Real-time kinetics of gene activity in individual bacteria," *Cell*, vol. 123, no. 6, pp. 1025–1036, 2005.

[49] M. Kanehisa and S. Goto, "KEGG: Kyoto encyclopedia of genes and genomes," *Nucleic acids research*, vol. 28, no. 1, p. 27, 2000.

[50] H. Kim, R. Atalay, and E. Gelenbe, "G-Network Modelling Based Abnormal Pathway Detection in Gene Regulatory Networks," *Computer and Information Sciences II*, pp. 257–263, 2011.

[51] H. Kim and E. Gelenbe, "Anomaly detection in gene expression via stochastic models of gene regulatory networks," *BMC genomics*, vol. 10, no. Suppl 3, p. S26, 2009.

[52] ——, "G-network based two layer stochastic modeling of gene regulatory networks with post-translational processes," *Interdisciplinary Bio Central*, vol. 3, pp. 8–12, 2011.

[53] ——, "Stochastic Gene Expression Modeling with Hill Function for Switch-like Gene Responses," *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, vol. 9, no. 4, pp. 973–979, 2012.

[54] T. Kocak, J. Seeber, and H. Terzioglu, "Design and implementation of a random neural network routing engine," *Neural Networks, IEEE Transactions on*, vol. 14, no. 5, pp. 1128–1143, 2003.

[55] J. Little and M. Gellert, "The SOS regulatory system: control of its state by the level of RecA protease," *Journal of Molecular Biology*, vol. 167, no. 4, pp. 791–808, 1983.

[56] N. Marianayagam, M. Sunde, and J. Matthews, "The power of two: protein dimerization in biology," *Trends in Biochemical Sciences*, vol. 29, no. 11, pp. 618–625, 2004.

[57] H. McAdams and A. Arkin, "Stochastic mechanisms in gene expression," pp. 814–819, 1997.

[58] J. Paulsson, "Models of stochastic gene expression," *Physics of Life Reviews*, vol. 2, no. 2, pp. 157–175, 2005.

[59] J. Paulsson, O. Berg, and M. Ehrenberg, "Stochastic focusing: fluctuation-enhanced sensitivity of intracellular regulation," *Proceedings of the National Academy of Sciences*, vol. 97, no. 13, p. 7148, 2000.

[60] P. Smolen, D. Baxter, and J. Byrne, "Modeling circadian oscillations with interlocking positive and negative feedback loops," *Journal of Neuroscience*, vol. 21, no. 17, p. 6644, 2001.

[61] K. Sneppen, S. Krishna, and S. Semsey, "Simplified Models of Biological Networks." *Annual review of biophysics*, 2010.

[62] N. Strelkowa and M. Barahona, "Switchable genetic oscillator operating in quasi-stable mode," *Journal of The Royal Society Interface*, vol. 7, no. 48, pp. 1071–1082, 2010.

[63] M. Thattai and A. van Oudenaarden, "Intrinsic noise in gene regulatory networks," *Proceedings of the National Academy of Sciences*, vol. 98, no. 15, p. 8614, 2001.

[64] M. Tigges, T. Marquez-Lago, J. Stelling, and M. Fussenegger, "A tunable synthetic mammalian oscillator," *Nature*, vol. 457, no. 7227, pp. 309–312, 2009.

[65] R. Varadhan and P. Gilbert, "Bb: An r package for solving a large system of nonlinear equations and for optimizing a high-dimensional nonlinear objective function," *Journal of Statistical Software*, vol. 32, no. 4, pp. 1–26, 2009.

[66] W. Weber and M. Fussenegger, "Molecular diversity–the toolbox for synthetic gene switches and networks," *Current Opinion in Chemical Biology*, 2011.

[67] D. Wilkinson, *Stochastic modelling for systems biology*. Chapman & Hall/CRC, 2006.

[68] F. Wu, "Stability and bifurcation of ring-structured genetic regulatory networks with time delays," *Circuits and Systems I: Regular Papers, IEEE Transactions on*, no. 99, pp. 1–9, 2011.