Estimating the Molecular Information Through Cell Signal Transduction Pathways

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***Abstract*— The development of reliable abstractions, models, and characterizations of biochemical communication channels that propagate information from/to biological cells is one of the first challenges for the engineering of systems able to pervasively interface, control, and communicate through these channels, *i.e.*, the Internet of Bio-Nano Things. Signal transduction pathways in eukaryotic cells are important examples of these channels, especially since their performance is directly linked to organisms' health, such as in cancer. In this paper, a novel computational approach is proposed to characterize the communication performance of signal transduction pathways based on chemical stochastic simulation tools, and the estimation of information-theoretic parameters from sample distributions. Differently from previous literature, this approach does not have constraints on the size of the data, accounts for the information contained in the dynamic pathway evolution, and estimates not only the end-to-end information propagation, but also the information through each component of the pathway. Numerical examples are provided as a case study focused on the popular JAK-STAT pathway, linked to immunodeficiency and cancer.**

***Index Terms*—Molecular Communication, Information Theory, Cell Signal Transduction Pathways, Gillespie Stochastic Simulation, Internet of Bio-Nano Things, Nanonetworks**

I. Introduction

The Internet of Bio-Nano Things (IoBNT) has been recently proposed by stemming from a direct contamination of theory and tools between cutting-edge branches of biology and communication engineering, with the promise of developing systems able to extend the Internet cyberspace to the biochemical domain, and operate a pervasive sensing and control of the biochemical processes at the basis of life [1]. The most important and immediate applications of such systems are in the biomedical field [2], where our ever increasing understanding of physiological processes involving our cells is also resulting into a growing awareness of their complexity, and the need of sophisticated systems to interact with them. We believe that one of the first challenges in this direction is to develop reliable abstractions, models, and characterizations of the biochemical reality underlying these processes with tools and concepts from communication theory, able to bridge cultural and technological gaps and enable the engineering of IoBNT-based devices and systems.

One of the best candidates to study, characterize, and eventually control and engineer the communication of information in the cellular realm is the cell's natural ability to sense information from the environment through signal-relaying biochemical reactions, *i.e.*, signal transduction pathways, [3] which are at the basis of major cellular functionalities, and whose performance can affect organisms' health, such as in cancer formation and progression [4]. In particular, the communication theoretic study of signal transduction pathways in eukaryotic cells, which propagate information to the cell's nucleus, such as the JAK-STAT pathway [5] considered as a case study in this paper, is particularly valuable in light of the latest advancements in mammalian synthetic biology [6], where novel genetic engineering tools are enabling a precise and dynamic control of the underlying biochemical processes.

In this paper, we aim at characterizing the performance of signal transduction pathways in terms of amount of information that is successfully propagated from the external environment to the cell's nucleus, as well as the amount of information handled by each process along the pathway. In other words, we estimate the point-to-point information transfer between chemical nodes along the pathway. For this, we abstract signal transduction pathways as complex communication channels characterized by non-linear behaviors, stochastic processes, feedback, and feedforward loops, and we propose a computational approach based on chemical stochastic simulation tools, and the estimation of information-theoretic parameters from sample distributions. This approach has fundamental differences from previous literature where mutual information calculation is applied to experimental data from signal transduction pathways [7], as detailed in Sec. III, and does not account for the time evolution of the pathway. In [8], the role of special pathway proteins is elucidated, but without a quantitative estimation of information flow.

The rest of the paper is organized as follows. In Sec. II we review the main processes at the basis of signal transduction pathways and propose our abstraction, in Sec. III we detail the proposed computational approach, and in Sec. IV we present a numerical case study based on the computational model of an important pathway. Finally, in Sec. V we conclude the paper.

II. Molecular-Information-Based Abstraction of Cell Signal Transduction Pathways

A. Overview of the Biochemical Processes

Signal transduction pathways are series of chained biochemical processes where molecules interact with each other to propagate physical or chemical signals through biological cells [3]. In particular, with reference to Fig. 1a, they most commonly propagate **extracellular signals** (embedded

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in physical or chemical parameters in the extracellular environment) into the cell, where the information they carry is utilized to accordingly regulate major cellular functionalities, such as the cell growth rate and cell division (**proliferation**), cell differentiation, cell death (**apoptosis**, **anti-apoptosis**), and cell physiological stability (**homeostasis**). This propagation is most commonly initiated at the **cell membrane** by special proteins (biological macromolecules with specific functions), called **receptors**, which are sensitive to extracellular signals by binding to information-bearing molecules from the extracellular environment. Upon these binding reactions, the receptors undergo a conformational change in the intracellular space, and initiate cascades of chemical reactions, *i.e.*, **protein-to-protein interactions**, where specific proteins, the kinases, get activated through the addition of a phosphate group (phosphorylation), and subsequently, possibly after binding to other protein into complexes, activate other proteins downstream of the cascade. Other specific proteins, the phosphatases, "reset" the activated proteins along the cascade by removing the aforementioned phosphate group (dephosphorylation). These cascaded reactions triggered by the initial extracellular signal result in the overall propagation of the information through reaction chains, which ultimately results into the activation of **transcription factors**, which are other proteins that, when active, are able to regulate the aforementioned cellular functionalities by increasing (induced) or decreasing (repressed) the **expression** of one or more **downstream DNA genes** inside the cell **nucleus** [9]. Through these biochemical processes, the initial information contained in the concentration of extracellular molecules is transduced into the concentration of bound receptors, which is in turn transduced into the concentration of activated kinases and protein complexes along the reaction cascade, and finally into the concentration of activated transcription factors. As depicted in Fig. 1a, these processes result in an overall flow of this information from the environment, through the signal transduction pathway, finally reaching the regulation of gene expression. In this paper, we abstract and model this flow of molecular information through each of the aforementioned processes in signal transduction pathways by utilizing tools from communication and information theory, and computational biology.

B. Molecular Information Abstraction

In this paper, we abstract the aforementioned biochemical processes underlying cell signal transduction pathways as communication channels that propagate the **input information** from extracellular signals to **each protein of the pathway**, which ultimately relay this information as **output information** to the transcription factors in the cell nucleus, as sketched in Fig. 1b. Our aim is to provide a quantitative characterization of this information as it flows through the signal transduction pathway, and we rely on the following assumptions commonly accepted in computational biology literature:

- The concentrations of all the aforementioned molecular species are considered homogeneous at any time instant outside the cell membrane (information-bearing molecules), at the cell membrane (receptors), inside the cell membrane

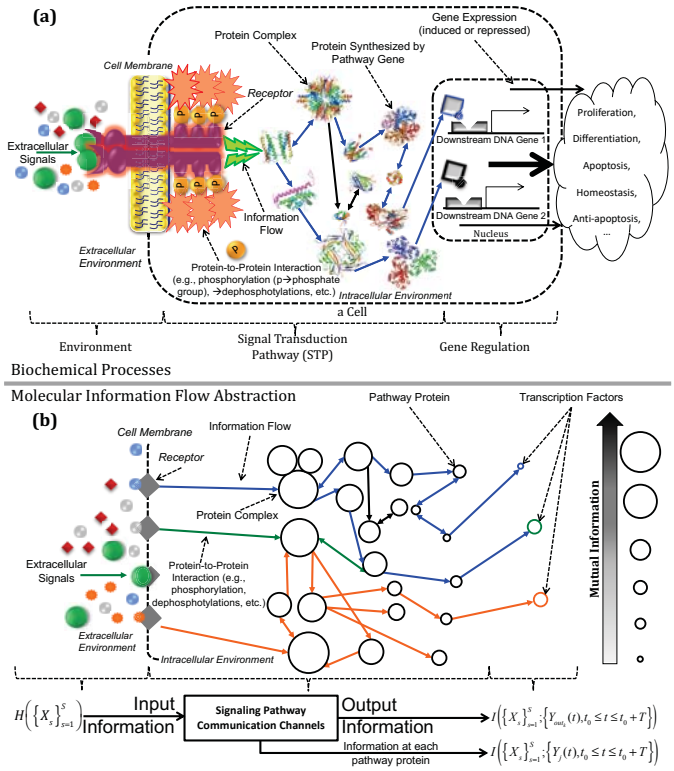

Fig. 1: Pictorial sketch of the biochemical processes in cell signaling pathways (a). Proposed molecular information flow abstraction (b).

(phosphorylating proteins), and inside the cell nucleus (possibly other phosphorylating proteins, transcription factors), respectively. This assumption corresponds to a compartmentalized well-stirred system in chemical modeling [10].

- Each chemical reaction in the pathway, expressed in general as $\mathrm{A}+\mathrm{B} \underset{\mathrm{k_r}}{\overset{\mathrm{k_f}}{\rightleftharpoons}} \mathrm{C}+\mathrm{D}$, where A, B are the reactant molecule species, C, D are the product molecule species, and k_f and k_r and the forward and reverse reaction rates, respectively (for irreversible reactions $k_r = 0$ and the backward arrow is omitted, and B and/or D can be omitted depending on the reaction), is modeled mathematically through mass action kinetics as follows [10]: $\frac{d[C](t)}{dt} = k_f[A](t)[B](t) - k_r[C](t)[D](t)$, where $[.](t)$ denotes the concentration of the molecule species as function of the time t. The same expression is valid by substituting $[D](t)$ in place of $[C](t)$. In the pathway picture of Fig. 1b, each circle represents a reactant or product molecule species, and each arrow corresponds the molecule specie participation to a chemical reaction. These molecule species might be subject to degradation reactions, expressed as $\mathrm{A} \xrightarrow{\mathrm{k_d}} 0$, where k_d is the degradation rate, and action kinetics formulation as $\frac{d[A](t)}{dt} = -k_d[A](t)$. Chemical reactions are affected by noise according to the Chemical Master Equation (CME) [10], [11], which can be computationally implemented through the Gillespie's Stochastic Simulation Algorithm (SSA) [12].
- The input concentration of information-bearing molecules in the extracellular environment $X_s(t)$, where s is a molecular species out of S extracellular signals, is the result of a

molecule source in the extracellular environment (another cell or a dose provided to the cell culture during an experiment), which consequently varies the concentration $X_s(t_0)$, where t_0 corresponds to an initial state of the system, by an amount $\overline{X}_s$, whose value corresponds to the input information, which is kept constant during the propagation of this information through the pathway. This models the situation where in a lab experiment a chemical reagent is added to a cell culture in a determinate quantity [7]. The output concentration of transcription factors $Y_{out_k}(t)$, as well as the concentration of all the proteins involved in the aforementioned cascaded reactions of the pathway $Y_j(t)$, are in general functions of the time t. We define T as the time interval necessary for all these concentrations to reach a steady-state regime (constant or periodic).

In agreement with the aforementioned assumptions, Fig. 1b captures the abstraction of the information flow in a typical cell signaling pathway, as we propose in this paper. In particular, the **Input Information** is carried by a change at time t_0 in the extracellular concentrations of information-bearing molecules at the input of the signal transduction pathway, quantified through the entropy expression $H\left(\{X_s\}_{s=1}^{S}\right)$. This information is propagated through the signal transduction pathway by the modulation of the interactions between the pathway proteins, which result into a time evolution of the concentration of each of these proteins within the aforementioned time interval T. Biological noise and other effects [13] tend to decrease the information content in the protein interaction modulation by randomization or equivocation [14] during its propagation in the signaling pathway, resulting in a residual **information at each pathway protein**, quantified through the Mutual Information (MI) $I_j = I\left(\{X_s\}_{s=1}^{S}; \{Y_j(t), t_0 \leq t \leq t_0+T\}\right)$ at protein j. Finally, the protein-protein interaction modulation through the pathway is transduced into the modulation of the concentration of each downstream transcription factor k, $k = 1, \ldots, K$, which is the **Output Information** of the pathway, quantified through the MI $I_{out_k} = I\left(\{X_s\}_{s=1}^{S}; \{Y_{out_k}(t), t_0 \leq t \leq t_0+T\}\right)$. In Fig. 1b, and in the rest of the paper, this information flow is graphically depicted for each pathway protein as a circle with area proportional to the corresponding MI.

III. Estimating the Molecular Information

In this paper, we detail a methodology to estimate the aforementioned molecular information flow parameters starting from the knowledge of the chemical reactions of the pathway, and their kinetic rates, as expressed in Sec. II-B. For this, we take into account that in general the signaling pathway communication channels as defined above are characterized by the non-linearity of chemical reactions, and the effect of feedforward, and feedback loops in the pathway reaction cascade [15], which, together with the aforementioned CME noise [10], do no allow for a closed-form analytical expression of the MI parameters. As a consequence, in this paper we devise a computational approach based on the stochastic simulation of chemical reaction kinetics through the aforementioned SSA [12]. Based on this simulation methodology, we estimate the MI by collecting and analyzing data, inspired by the procedure in [7], [15] with the following three main differences: i) we are based on a computational simulation rather than expensive wet lab experiments, which does not pose stringent constraints on the size of the data set that can be collected; ii) we estimate the MI taking into account the complete time evolution of the output, instead of only accounting for a single value of the output in a dose-response characterization, often made in experimental studies, such as in [7]; iii) we perform the MI estimation not only at the pathway output, but also at each protein and protein complex.

For simplicity of notation, in the following we will consider a pathway having only one species of information-bearing molecules at the input ($S = 1$), and only one type of output transcription factors ($K = 1$). All the following expressions can be generalized to scenarios with multiple inputs/outputs.

A. Computational Approach

1) Goal: The final goal of our computational approach is the estimation of the MI $\tilde{I}_j$ at each pathway protein j, expressed as

$$\tilde{I}_j = \tilde{H}(X) - \tilde{H}(X|\,\{Y_j(t), t_0 \leq t \leq t_0+T\})\,, \qquad (1)$$

where $H(.)$ and $H(.|.)$ denote the estimated entropy and conditional entropy, respectively, X is the input concentration of information-bearing molecules, and $\{Y_j(t), t_0 \leq t \leq t_0+T\}$ is the time evolution of the concentration of the pathway protein $Y_j(t)$ within a time interval T from t_0. The estimation of the output MI $\tilde{I}_{out}$ is expressed as in (1) and in the subsequent equations by substituting out in place of j.

2) Details: The necessary *data for the MI estimations* is obtained through SSA simulations of the chemical reactions of the pathway [12]. In particular, for each value x_i, $i = 0, \ldots, I$, of the input concentration X sampled from the range between x_{min} and x_{max}, defined here as the value below which the concentrations of any pathway protein do not significantly change, and the value above which the same concentrations do not show noticeable changes in their time evolution, we run a total of R simulations. Each SSA simulation is run independently, and starts at the same steady state that the system reaches with an input concentration value $X = 0$.

The *estimated input entropy* $\tilde{H}(X)$ is computed through the histogram approach [16] as

$$\tilde{H}(X) = -\sum_{i=1}^{I} p_X(x_i) \log_2\left(\frac{p_X(x_i)}{w_X}\right)\,, \qquad (2)$$

where $p_X(x_i) = 1/I$, according to the simplifying assumption of having a uniformly distributed input, in agreement with [7], and w_X is the sampling interval $(x_{max} - x_{min})/I$.

The *estimated conditional entropy* $\tilde{H}(X|\,\{Y_j(t), t_0 \leq t \leq t_0+T\})$ of the input concentration X given

the time evolution of the concentration of the pathway protein j is computed as

$$\tilde{H}(X|\{Y_j(t), t_0 \le t \le t_0+T\}) = -\sum_{N_{j,t_0}}\sum_{N_{j,t_1}}\cdots\sum_{N_{j,t_N}} p_{Y_j}\left(\{y_{j,t_n}\}_{n=0}^{N}\right) \sum_{s=1}^{S_{\{y_{j,t_n}\}_{n=0}^{N}}} p_{X|\{y_{j,t_n}\}_{n=0}^{N}}(x_s) \log_2\left(\frac{p_{X|\{y_{j,t_n}\}_{n=0}^{N}}(x_s)}{w_{X,\{y_{j,t_n}\}_{n=0}^{N}}}\right), \quad (3)$$

where $t_N = t_0 + T$, N being the number of time samples considered when discretizing $Y_j(t)$ within the interval T (for computational processing), $\{y_{j,t_n}\}_{n=0}^{N}$ is a set of values of the protein concentration $Y_j(t)$ at time instants $t_0, t_1, \ldots, t_N$, N_{j,t_n} is the number of histogram bins considered for the protein concentration value $Y_j(t_n)$ to compute the multidimensional histogram p_{Y_j}, $S_{\{y_{j,t_n}\}_{n=0}^{N}}$ and $w_{X,\{y_{j,t_n}\}_{n=0}^{N}}$ are the number and the size of histogram bins considered for the input concentration X to compute the histogram $p_{X|\{y_{j,t_n}\}_{n=0}^{N}}(x_s)$, where $w_{X,\{y_{j,t_n}\}_{n=0}^{N}} = (x_{max} - x_{min})/S_{\{y_{j,t_n}\}_{n=0}^{N}}$ and x_s is a value from the concentration input $\{x_i\}_{i=0}^{I}$ sampled according to the histogram. The numbers of histogram bins N_{j,t_n} are computed from the aforementioned simulation data according to the Doane's formula [16] as follows:

$$N_{j,t_n} = 1 + \log_2(C) + \log_2\left(1 + \frac{g_{Y_j(t_n)}}{\sigma_{g_{Y_j(t_n)}}}\right). \quad (4)$$

where $C = I * R$ is the total number of simulation runs, $g_{Y_j(t_n)}$ is the estimated 3rd-moment-skewness of the distribution $p_{Y_j(t_n)}$ from the simulation data, and $\sigma_{g_{Y_j(t_n)}} = \sqrt{\frac{6(C-2)}{(C+1)(C+3)}}$. The number of histogram bins $S_{\{y_{j,t_n}\}_{n=0}^{N}}$ is computed with a similar expression as in (4) by substituting $Y_j(t_n)$ (and C) with the set of x_i values (number of x_i values) that resulted in a concentration evolution for protein j equal to $\{y_{j,t_n}\}_{n=0}^{N}$. Finally, the probabilities p_{Y_j}, for all the J pathway proteins, and $p_{X|\{y_{j,t_n}\}_{n=0}^{N}}$, for all the combination of values y_{j,t_n} at each time instant t_n of each of the J pathway proteins, are computed as histogram distributions of the aforementioned data according to Algorithm 1. In Fig. 2 we show a graphical example of the computation of $\left(\{Z_{i,r}\}_{t_n}, b_{t_n}\right)$ as per Algorithm 1 for a protein in the case study pathway detailed in Sec. IV, where we consider the results of multiple simulation runs for different input concentrations, and overlay at t_n the N_{j,t_n} equally-spaced bins between min and max values.

IV. Numerical Results for the JAK-STAT Pathway

In the following, we present the results of the computational approach detailed in Sec. III-A when applied to a specific signal transduction pathway, *i.e.*, the JAK-STAT pathway. This pathway was chosen because: i) it is relatively simple and small with respect to other signal transduction pathways in eukaryotic cells; ii) its complete kinetic model with the chemical reactions of the pathway and each k_f, k_r, k_d, defined in Sec. II-B, is publicly available in the BioModels Database [17]; iii) the dysregulation of JAK-STAT pathway has been linked to immunodeficiencies and cancers.

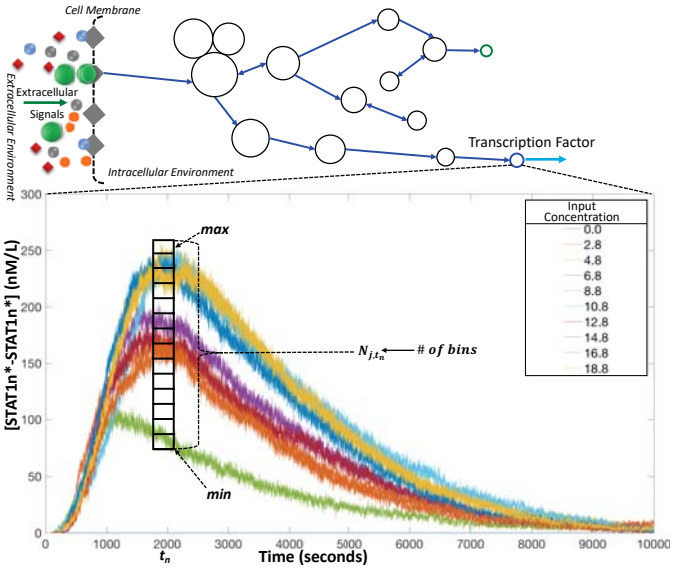

Fig. 2: Graphical sketch of the computation of Steps 1-4 of Algorithm 1 for the phosphorylated and dimerized output transcription factor STAT1n*-STAT1n* of the JAK-STAT pathway.

Algorithm 1: Probability Histograms for Equation (3)

Data: R simulation runs for each of I input concentrations containing values for all N simulation steps
Result: For each protein j, p_{Y_j} and $p_{X|\{y_{j,t_n}\}_{n=0}^{N}}$

1 **for** *each simulation time step* t_n **do**
2 Create $\{Z_{i,r}\}_{t_n}$ by extracting protein j concentration for each simulation run r and input concentration i
3 Map each value of $\{Z_{i,r}\}_{t_n}$ in N_{j,t_n} equally-spaced bins (with index b_{t_n}) between min and max values, expressed as $\left(\{Z_{i,r}\}_{t_n}, b_{t_n}\right)$
4 **end**
5 Obtain matrix M of size C by N by combining all the mapped bin indices b_{t_n} for each simulation run (i,r) and each time step t_n
6 Compute the multidimensional histogram considering each row of M as a datapoint: $p_{Y_j}\left(\{y_{j,t_n}\}_{n=0}^{N}\right)$
7 **for** *each bin in the multidimensional histogram* **do**
8 Take all the input values corresponding to the values $\{y_{j,t_n}\}_{n=0}^{N}$ that define the current multidimensional bin
9 Compute the histogram $p_{X|\{y_{j,t_n}\}_{n=0}^{N}}$ by mapping the input values found at Step 8 into $S_{\{y_{j,t_n}\}_{n=0}^{N}}$ equally space bins between min and max values
10 If no input value from Step 8, set $p_{X|\{y_{j,t_n}\}_{n=0}^{N}} = 0$
11 **end**

As shown in Fig. 3, the JAK-STAT kinetic model that we utilize to compute the numerical results of this paper consists of $J = 34$ chemical species (proteins) and 46 reactions, and its complete description and parameter values can be found in [17], [18]. In this model, the input is the concentration of a small signaling protein called interferon gamma (IFN-γ/IFN-green node) while the output is the phosphorylated transcription factor STAT1n*-STAT1n* (blue node). In Fig. 3 we show the complete interconnections between different protein species, and proteins at different phosphorylation (denoted

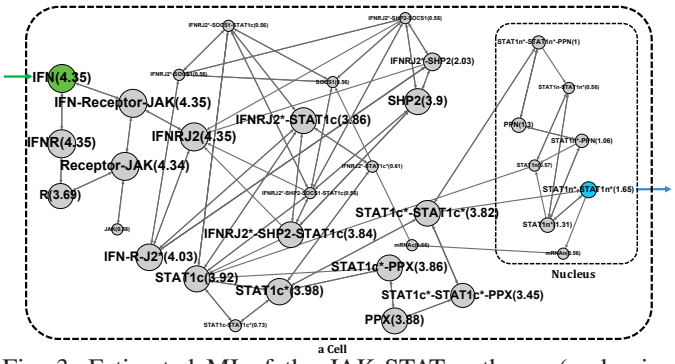

Fig. 3: Estimated MI of the JAK-STAT pathway (node size proportional to MI value in [bits]).

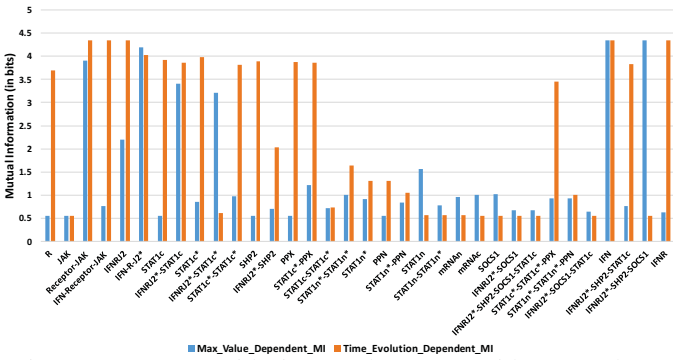

Fig. 4: Comp. MI with time evol. Vs. MI with max values.

with a * when phosphorylated) or binding (dashed or denoted by their initials) states involved in reactions.

To obtain the data necessary for our computational approach, we utilized the implementation of the SSA algorithm in Matlab Simbiology. Through these simulations, the values of x_{min} and x_{max}, defined in Sec. III-A2, were found to be 0 and 20 nmol/litre, respectively. For simplicity, we considered a number $I = 51$ different input concentrations, resulting in a sampling interval $w_X = 0.4$ nmol/litre. For each input concentration, we arbitrarily run $R = 100$ independent simulations for a time interval $T = 10,000$ seconds, estimated as defined in Sec. II-B. The time step of each simulation is set to $t_n - t_{n-1} = 1$ second (N = 10,000). In Fig. 2 we show the simulation results for the phosphorylated and dimerized output transcription factor STAT1n*-STAT1n* at each time step for only one of the R runs for a restricted number of input concentrations out of I.

The MI values for each pathway protein estimated from the simulation data through the computational approach in Sec III-A is reported in Fig. 3, and graphically shown in a corresponding proportional size of each graph node (protein). As expected, the value of MI is decreasing as it propagates through the reaction cascades, accumulating chemical noise at each reaction (data processing inequality [14]), from an estimated input entropy $\tilde{H}(X) = 4.35$ bits to an estimated output MI $\tilde{I}_{out} = 1.65$ bits. In Fig. 4 we show a comparison bar chart between the MI of Fig. 3 estimated by taking into account the time evolution $\{Y_j(t), t_0 \leq t \leq t_0 + T\}$ of each protein concentration, and an MI similarly estimated, but only taking into account the maximum value $\max_{t_0 \leq t \leq t_0+T} Y_j(t)$. As expected, the latter generally underestimates the MIs.

V. Conclusion

In this paper, we proposed a computational approach to characterize the performance of signal transduction pathways in terms of amount of information that is successfully propagated from the external environment to the cell's nucleus, as well as the amount of information handled by each protein along the pathway. This approach is a preliminary yet very important step in understanding how communication theory tools can be applied to obtain novel information from signal transduction pathways, such as the importance of a pathway process in relying information through the pathway, and how this is correlated in case of diseases (e.g., cancer) to possible impairments to the functionality of the same protein (e.g., mutation of the corresponding protein-encoding genes).

Acknowledgment

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