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Analysis of IL6 Signal Transduction Model using Reduced Rank Regression

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Abstract—This work presents the application of reduced rank regression to the field of systems biology. A computational approach is used to investigate the mechanisms of the janus-associated kinases/signal transducers and transcription factors (JAK/STAT) and mitogen activated protein kinases (MAPK) signal transduction pathways in hepatic cells stimulated by interleukin-6. The results obtained identify the contribution of individual reactions to the dynamics of the model. These findings are compared to previously available results from sensitivity analysis of the model which focused on the parameters involved and their effect. This application of reduced rank regression allows for an understanding of the individual reaction terms involved in the modelled signal transduction pathways and has the benefit of being computationally inexpensive. The obtained results complement existing findings and also confirm the importance of several protein complexes in the MAPK pathway which hints at benefits that can be achieved by further refining the model.

I. INTRODUCTION

Research on the molecular mechanisms of signal transduction is a very important topic that has attracted significant interest from biologists, bioengineers and biotechnologists. Although considerable progress in the identification of the molecular components involved in cell functions has been made over the past decades, the underpinning molecular mechanisms remain largely unknown and poorly understood.

This paper analyzes an available model of signal transduction pathways in hepatic cells when stimulated by interleukin-6 (IL6) [1]. From the associated medical literature it is known that IL6 represents one of the principal factors involved in the regulation of most Acute Phase Proteins [2]. These are a product of the Acute Phase Response which is a beneficial short-term response to a tissue trauma, injury or infection in mammals [3].

Cytokines, such as IL6 are produced to stimulate complex intracellular signaling, resulting in the up and/or down regulation of specific plasma proteins, known as Acute Phase Proteins (APPs). A deeper understanding of the pathways and mechanisms involved can lead to the prevention or mediation of the problems that can occur under prolonged exposure to these elevated levels of plasma proteins [4],[5].

This work shows how to translate the underlying mechanistic model, describing the components involved in the signal transduction initiated by IL6, into a form that is linear in parameters. This can be taken advantage of in

representing this complex model by linear predictor/response interrelationships and allows conventional multivariate data analysis tools to be applied. Such techniques include Partial Least Squares (PLS), Canonical Correlation Analysis (CCA) and Reduced Rank Regression (RRR) which extract and discriminate dominantly contributing terms from those that describe marginal and therefore negligible information encapsulated in the predictor variable set [6].

The RRR estimator, pioneered by Anderson [7], is a projection method to analyze multivariate data sets with the aim of producing the most accurate regression model with as few linearly independent projection directions within the predictor space as possible. In contrast, CCA [8] and PLS [9] are techniques that produce projections of the observations within the predictor and response space that maximize a correlation and covariance criterion respectively and therefore analyze the underlying interrelationships completely in this projection, or latent variable, space. To determine which of the terms within the ordinary differential equations of the IL6 model are dominantly contributing to the prediction of the derivatives, RRR is consequently considered here. It is important to note that multivariate analysis techniques have not received significant attention in the field of systems biology as analysis tools for the study of such pathway models.

Previous work on analyzing such models include sensitivity analysis [10], which provides an insight into the importance of the parameters on the concentration of the transcription factor. RRR on the other hand will analyze the contribution of individual reaction terms to the dynamical changes exhibited by protein concentrations in the model. With these results it is possible to simplify the existing model as well as to gain a better understanding of the relevance of some reaction terms which can be further used to determine which parts of the model may warrant further model refinement.

Section II introduces preliminary information on reduced rank regression and is followed in Section III by a brief overview of the IL6 signal transduction model being analyzed. Section IV details how the data is generated, the assumptions involved and the required scaling. An in depth discussion of the results is presented in Section V and is followed by a concluding summary in Section VI.

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II. PRELIMINARIES

This section briefly reviews reduced rank regression which directly determines score variables as a linear combination of the predictor set that predict the response set with maximum accuracy. It is therefore the preferred technique over competitive multivariate tools, such as CCA or PLS.

Given a predictor and response variable set $\mathbf{x} \in \mathbb{R}^N$ and $\mathbf{y} \in \mathbb{R}^M$, respectively, the cost function for minimizing the residual variance over a total of K observations is given by the Frobenius norm of:

$$\mathbf{E} = \mathbf{Y} - \mathbf{t}\mathbf{t}^T\mathbf{Y} \quad (1)$$

where $\mathbf{Y} \in \mathbb{R}^{K \times M}$ is the response matrix, $\mathbf{E} \in \mathbb{R}^{K \times M}$ is the residual matrix, $\mathbf{t} = \mathbf{X}\mathbf{w}$ is the score vector, $\mathbf{X} \in \mathbb{R}^{K \times N}$ is the predictor matrix, $\mathbf{w} \in \mathbb{R}^N$ is the weight vector and K is the number of observations. This produces the following cost function:

$$\|\mathbf{E}^T\mathbf{E}\|_2^2 = \|\mathbf{Y}^T[\mathbf{I} - \mathbf{t}\mathbf{t}^T]\mathbf{Y}\|_2^2, \quad (2)$$

which is subject to the following constraints:

$$\mathbf{t} = \mathbf{X}\mathbf{w} \quad \|\mathbf{t}\|_2^2 - 1 = 0. \quad (3)$$

The solution of this constrained optimization problem is given by:

$$\left[[\mathbf{X}^T\mathbf{X}]^\dagger \mathbf{X}^T\mathbf{Y}\mathbf{Y}^T\mathbf{X} - \lambda\mathbf{I} \right] \mathbf{w} = \mathbf{0} \quad (4)$$

where † represents the generalized inverse.

Based on the work by Golub [11] on computationally efficient and numerically stable solutions for CCA, the following steps can be applied to obtain the $n = \min\{M, N\}$ weight vectors (LVs), stored in $\mathbf{W}$.

Step	Equation	Description
1	$\Sigma_{XX} = \mathbf{X}^T\mathbf{X}$	Cross product matrix for predictor set
2	$\Sigma_{XY} = \mathbf{X}^T\mathbf{Y}$	Cross product matrix for predictor and response sets
3	$\Sigma_{XX} = \mathbf{U}_X\mathbf{L}_X\mathbf{V}_X^T$	Singular value decomposition of Σ_{XX}
4	$\Sigma_{XX}^{-1/2} = \mathbf{U}_X\mathbf{L}_X^{-1/2}\mathbf{V}_X^T$	Square root of inverse of Σ_{XX}
5	$\mathbf{S} = \Sigma_{XX}^{-1/2}\Sigma_{XY}$	Set-up matrix product
6	$\mathbf{S} = \mathbf{U}\mathbf{R}\mathbf{V}^T$	Singular value decomposition of $\mathbf{S}$
7	$\mathbf{W} = \Sigma_{XX}^{-1/2}\mathbf{U}$	Compute weight vectors

TABLE I

STEPS REQUIRED IN THE COMPUTATION OF WEIGHT VECTORS

III. IL6 SIGNAL TRANSDUCTION IN HEPATOCYTES

The signaling pathway model to be analyzed describes signal transduction in hepatocytes when stimulated by IL6. This model integrates signaling through the JAK/STAT and MAPK pathways. It consists of 68 nonlinear ordinary differential equations (ODEs) which can be represented by:

$$\frac{d\mathbf{x}}{dt} = f(\mathbf{x}, \mathbf{p}, u) \quad (5)$$

The equations are concentration balances of individual proteins and protein complexes and are derived according to the law of mass action or Michaelis-Menten kinetics. The parameters, $\mathbf{p}$, represent the reaction constants, the states, $\mathbf{x}$, are the concentrations of the proteins in the pathway and the input, u , is the stimulating concentration of IL6. A detailed description of the model can be found in [1].

IV. DATA GENERATION

This section details the determination of the state sequences and their respective derivative terms. The simplification of the Michaelis-Menten Kinetics is explained and the construction of the predictor and response variables presented. The input sequence of the stimulating IL6 concentration is described and is followed by a brief discussion of the scaling of the data sets.

A. Determination of State Sequences

The state sequences are obtained by solving the set of 68 nonlinear ordinary differential equations and sampling the data every minute so that the fastest response in the system, which is in the region of 30 minutes, is captured.

The differential terms are then calculated for each consecutive data point by substituting the corresponding values of the state variables into the ODEs. These differential terms make up the response matrix $\mathbf{Y} \in \mathbb{R}^{K \times M}$, where M is the number of derivative terms, which is 68.

The predictor matrix $\mathbf{X} \in \mathbb{R}^{K \times N}$ is constructed of each of the cross product terms in the state space equations, where N refers to the number of cross product terms. Equation 6 presents the first three ODEs of the model and Equation 7 illustrates how these cross products form the elements of the response matrix.

$$\begin{aligned} dx_1 &= -k_{f0}x_1u + k_{r0}x_2 \\ dx_2 &= k_{f0}x_1u - k_{r0}x_2 + k_{r2}x_6 - k_{f2}x_2x_5 \\ dx_3 &= -k_{f1}x_3x_4 + k_{r1}x_5 \end{aligned} \quad (6)$$

$$\mathbf{X} = \begin{bmatrix} \mathbf{x}_1\mathbf{u} & \mathbf{x}_2 & \mathbf{x}_2\mathbf{x}_5 & \mathbf{x}_3\mathbf{x}_4 & \mathbf{x}_5 & \mathbf{x}_6 & \cdots \end{bmatrix} \quad (7)$$

B. Simplification of Michaelis-Menten Kinetics

Of the 68 ordinary differential equations, 3 contain rational fraction functions derived from Michaelis-Menten Kinetics. These need to be rewritten in a linear parametric representation. Equation 8 shows an example of how this simplification is performed.

$$\begin{aligned} \frac{dx_{25}}{dt} &= \frac{k_{18a}x_{20}}{k_{18b} + x_{20}} - k_{19}x_{25} \\ \frac{dx_{25}}{dt} + \frac{x_{20}}{k_{18b}} \frac{dx_{25}}{dt} &= \frac{k_{18a}}{k_{18b}}x_{20} - k_{19}x_{25} - \frac{k_{19}}{k_{18b}}x_{20}x_{25} \end{aligned} \quad (8)$$

As a result of this simplification, there will be some exclusion in the terms of the response matrix leading to the following linear regression model

$$\tilde{\mathbf{Y}} = \tilde{\mathbf{X}}\mathbf{B} \quad (9)$$

where $\tilde{\mathbf{X}} \in \mathbb{R}^{K \times N}$ is the predictor matrix, $\tilde{\mathbf{Y}} \in \mathbb{R}^{K \times M}$ is the response matrix and $\mathbf{B} \in \mathbb{R}^{M \times N}$ is the regression matrix which consists of the first order rate constants and Michaelis constants.

The predictor matrix consists of 94 cross product terms, consisting of those which appear in the 65 state space equations which have been derived solely from the law of mass action, and those from the remaining 3 rearranged ODEs which previously contained the rational fractions.

C. Input Signal

In order to properly excite the system (model), the input consists of a series of steps. The range for the IL6 concentration is selected based on the values previously and currently being used in experiments which is 0.00383nM to 0.383nM. By using an input succession of 60 steps from 0.001nM to 0.4nM a realistic range for the input concentration is maintained.

From the dynamic profiles of the state variables it is visible that the most dominant responses arise within the first 2 hours. There is very little response after 8 hours but slight changes can still be observed 100 hours after the initial stimulation. These long term changes seen in the model have no biological significance and are not seen in experimental results. The simulated model, as is the case with the real system, has no true steady state so, for this analysis, it is assumed that a complete steady state is achieved within 100 hours, with the most significant results occurring within the first 10 hours.

Therefore, when selecting the time to apply each step input, the first 50 steps focus on the range 0.1 hours to 15 hours, which corresponds to 0.2 times the shortest response [0.5 hours] and 1.5 times the longest response [10 hours] and the final 10 steps run for 100 hours. This ensures that each variable can reach the assumed steady state as well as be excited properly.

D. Scaling

To ensure the resulting predictor and response data sets are comparable they are scaled by their mean values and further scaled by dividing or multiplying the elements by a scalar value until the standard deviation of the data sets are comparable.

V. ANALYSIS OF PATHWAY MODEL

The results are analyzed by looking at the information provided from the first 19 dominant latent variables which reconstruct 95% of the response matrix, as can be seen in Table II. The information associated with the subsequent latent variables is negligible and can be disregarded.

Fig. 2. Relative value of the cumulative sum of the predictor variable weights for the 19 dominant latent variables.

A. Weight Vectors

The weight vectors are scaled to be of unit length and Figure 1 shows the relative values of these scaled weights assigned by each of the 19 dominant latent variables.

The weight vectors reveal the interrelationships between both the predictor and response variables. Terms with a greater weight can be identified as those which cause a significant change in the state variables and therefore indicate that they play an important role in the model. Conversely, those terms which have a lower weight may be recognized as causing a lesser change in the state variables and consequently producing a minor and possibly negligible change in the system.

In order to simplify the analysis a summation of the weights for each respective predictor term can be made. The results of this can be seen in Figure 2, where the cumulative sum of the w-weights are displayed as relative values.

15% of the components have a relative cumulative weight greater than 0.3. These terms are discussed in further detail in Section V.B, whereas Section V.C analyzes the components

Number of Latent Variable	Contribution to Y	Total Contribution to Y
1	0.29307	0.29307
2	0.20072	0.49379
3	0.15277	0.64656
4	0.07347	0.72003
5	0.06371	0.78374
6	0.06076	0.84450
7	0.03932	0.88382
8	0.03317	0.91699
9	0.00976	0.92674
10	0.00551	0.93225
11	0.00331	0.93557
12	0.00306	0.93863
13	0.00166	0.94029
14	0.00138	0.94168
15	0.00132	0.94300
16	0.00108	0.94408
17	0.00082	0.94490
18	0.00075	0.94565
19	0.00048	0.94613

TABLE II
CONTRIBUTION TO Y FOR EACH LATENT VARIABLE

Fig. 1. Relative value of predictor variable weights for the 19 dominant latent variables.

in the bottom 15%, i.e. with a relative cumulative weight of less than 0.04.

B. Regulatory Mechanisms with Large Contributions

The 13 terms identified as producing the largest change in their associated state variables are presented in Table III, along with a description of each mechanism and the associated relative weight.

In first position, as the reaction responsible for causing the greatest change, is the dephosphorylation of ERK-P by Phosp3 to produce ERK. The surrounding stages involved in this reaction also appear in the top 15% of contributors.

Phosp3 is one of three proteins responsible for dephosphorylating components in the MAPK pathway. Phosp1 also appears in the top ten contributors where it converts Raf* to Raf. These proteins, Phosp1, Phosp2 and Phosp3, are essential for signaling to occur.

The second mechanism displaying a significant impact on the model is the reaction of the STAT3N* and STAT3N molecules. These components occur in the signaling pathway just after the deactivation of the phosphorylated nuclear STAT3 dimer by the phosphatase PP2.

The production of STAT3N*-STAT3N* is the final step in the signal transduction pathway and the regulation of the amount of the transcription factor will correlate with transcription of DNA and ultimately the translation into proteins. The production of this molecule also correlates to the regulatory mechanism involving SOCS3 which has also been identified in the top 15% of contributing terms. SOCS3 has an important role in the JAK/STAT pathway where it

acts as an inhibitor for signal transduction.

The dephosphorylation of the nuclear phosphorylated dimer by PP2 is also a necessary step before STAT3 can be returned to the cytosol, where it can remain in a deactivated state or be activated and used for further signaling.

The predictor terms in 3rd and 4th place form part of the the MAPK pathway and their reactions are closely related. ERK and MEK-PP react to produce ERK-MEK-PP. This signaling compound then goes on to finally produce MEK-PP and ERK-PP which travels to the nucleus of the cell.

The mechanism ranked in 7th place, which is a result of the reaction ranked in 8th, plays a crucial role for both the JAK/STAT and MAPK pathways. The phosphorylation of the (IL6-gp80-gp130-JAK)₂ complex is the last generic step before the JAK/STAT and MAPK pathways can be isolated from each other. There is a degree of competition for the receptor sites on this complex as it is used by both pathways simultaneously, therefore it can be considered to be in high demand. A small decrease in its concentration will result in reduced signaling on both pathways with the converse also applying.

Terms in places 9 and 10 describe the reaction and formation of (IL6-gp80-gp130-JAK)₂-SHP2*-Grb2-SOS-Ras-GDP which is the final point in the MAPK pathway when the signaling molecules are attached to the signaling receptors on the cell membrane.

C. Regulatory Mechanisms with Small Contributions

Cross product terms assigned with a small weight do not contribute greatly to the overall model and the changes they

	Predictor Term	Description	Relative Weight
1	x_{63x66}	ERK-P and Phosp3	1.00000
2	x_{21x22}	STAT3N* and STAT3N	0.76146
3	x_{62}	ERK-MEK-PP	0.75420
4	x_{57x61}	MEK-PP and ERK	0.73281
5	x_{52}	Raf*-Phosp1	0.66378
6	x_{50x51}	Phosp1 and Raf*	0.64443
7	x_7	(IL6-gp80-gp130-JAK)2	0.57129
8	x_{6x6}	IL6-gp80-gp130-JAK and IL6-gp80-gp130-JAK	0.55691
9	x_{36x41}	Ras-GDP and (IL6-gp80-gp130-JAK)*2-SHP2*-Grb2-SOS	0.54312
10	x_{42}	(IL6-gp80-gp130-JAK)*2-SHP2*-Grb2-SOS-Ras-GDP	0.53514
11	x_{68}	ERK-P-Phosp3	0.49512
12	x_{20x25}	STAT3N*-STAT3N* and mRNA-SOCS3N	0.32841
13	x_{67}	ERK-PP-Phosp3	0.31265

TABLE III
PREDICTOR TERMS WITH LARGEST CONTRIBUTIONS TO THE MODEL

cause may be sufficiently small such that replacing their state variables by constant values may be a possibility. Table IV shows those terms which were identified as having very little contributions.

The mechanism identified as causing the smallest change in the state variables is that of Grb2-SOS. Also, the predictor terms ranked as producing the 7th and 12th smallest contributions refer to interactions with Grb2 and Grb2-SOS, respectively.

The interaction between the signal receptor gp130 and JAK has been identified as causing a small change in the state variable. The interaction of JAK and gp130 is required for signaling to begin in both the JAK/STAT and MAPK pathways and if this did not occur then a major change in the outcome would be observed. The small change that has been associated with this interaction may be due to the common assumption that cell surface receptors are extremely high in number and that a change in this number could be considered as negligible. If this was in fact the case, then the model could be refined by removing these components as variables and replacing them with a constant value.

Unlike the other phosphatases in the MAPK pathway, the dephosphorylation of MEK-P by Phosp2 to produce MEK has been highlighted as the fifth and sixth least contributing reaction terms. In fact, the product of this dephosphorylation, MEK, and its reaction with Raf* to form MEK-Raf* does not appear to produce a large variation in the state variables either.

The reaction between Ras-GTP* and Raf* has also been identified as causing a small change in the over states. These components are formed when Ras-GTP and Raf react to produce Raf-Ras-GTP, which then splits into the above mentioned terms. Once formed, the model does not indicate a result formed by their recombination. Therefore, it is clear that such a reaction does not appear to cause a significant change in the results.

The STAT3C-STAT3C* dimer also appears in the bottom 15% of the contributing components. This mechanism is produced as a result of the dephosphorylation by PP1. Once formed, the current model does not account for any consequential signaling of the component, nor does it model

its subsequent breakdown into constituent parts. This suggests that either this variable can be removed completely from the model, assuming it is degraded in the cell, or the model can be expanded to include for the possible deactivation/activation of STAT3C-STAT3C* so it can once again have the molecular structure of a signaling compound.

Throughout this analysis it is assumed that the model is accurate and the initial conditions for the states suitably defined. Should any of these conditions be breached then the interpretation of the results may be different.

VI. CONCLUSIONS

A new application of Reduced Rank Regression has been presented providing an insight into the mechanisms of the IL6 signal transduction pathways in hepatocytes. The results identify the relative contribution of individual reaction terms to protein concentrations.

Since RRR is a linear method that efficiently produces results using a batch singular value decomposition (SVD), one advantage is that it is computationally inexpensive, numerically stable and produces a unique analytical solution, even for large models.

From previous literature, the transition of STAT3 between the nucleus and the cytoplasm has been described as playing a crucial role in signal transduction [12] and this has been observed both in this analysis and the recent sensitivity analysis on the same model.

Future work will deal with the application of RRR to an adapted version of this model, which includes an additional feedback loop in the MAPK pathway. The current model can also be modified to set selected terms, which were associated with the smallest weights, to constant values and through the recomputation of the state sequences an investigation can be performed to see if the change they cause is in fact negligible. An analysis of the dominant derivatives through the observation of the v-weight vectors can be carried out and further research is underway to review the application of other regression techniques to this and other versions of the IL6 signal transduction model in hepatocytes.

	Predictor Term	Description	Relative Weight
1	x_{38}	Grb2-SOS	0.00142
2	x_5	gp130-JAK	0.00446
3	x_{54}	MEK-Raf*	0.00583
4	x_{51x53}	Raf* and MEK	0.00945
5	x_{55x59}	MEK-P and Phosp2	0.01408
6	x_{60}	MEK-P-Phosp2	0.01431
7	x_{34x39}	Grb2 and (IL6-gp80-gp130-JAK)*2-SHP2*	0.02528
8	x_{39}	(IL6-gp80-gp130-JAK)*2-SHP2*	0.02533
9	x_{16x46}	(IL6-gp80-gp130-JAK)*2-SHP2 and SHP2*	0.02797
10	x_{3x4}	gp130 and JAK	0.03107
11	x_{49x51}	Ras-GTP* and Raf*	0.03525
12	x_{38x39}	Grb2-SOS and (IL6-gp80-gp130-JAK)*2-SHP2*	0.03547
13	x_{14}	STAT3C-STAT3C*	0.03690

TABLE IV
PREDICTOR TERMS WITH SMALLEST CONTRIBUTIONS TO THE MODEL

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