JES
Journal of Engineering Sciences
Vol 11, Issue 6, JUNE /2020
ISSN NO:0377-9254

MATRIX USED WITH PARTIAL DIFFERENTIAL EQUATIONS FOR DESIGN OF EXPERIMENTS

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Abstract:

Mathematical models have previously been developed, and used, to identify potential drug targets to treat human diseases. A new study of IL-6 is generalized to predict acute step protein expression dynamics. Experimental data presented in the analysis of unknown model parameters are then validated with independent experimental data reported and based on the model developed for sensitivity testing, to identify reactions which play an important role in the regulation of haptoglobin, fibrinogen, and albumin dynamics. Molecular elements involved in these reactions are known to be possible targets for medicines. The D-optimacy criterion was used as the objective function of the experimental design problem, based on the Fisher knowledge matrix and separately a sensitivity matrix determined using the morris test. Optimal input functions have been defined by solving the optimal experimental design problem for model parameters estimation, and the resulting input functions have been demonstrated in simulation experiments to substantially reduce parameter unsecurity. Fairly, even though their existence was not limited, the defined optimum input function took the form of PRBS signals. Even though there were no restrictions on their nature. Future work should corroborate these findings by applying the determined optimal experimental design on a real experiment.

Keywords: optimal experimental design; Fisher information matrix; sensitivity analysis;

1.0 Introduction:

To explain and forecast the response of cells to such stimuli, mathematical models for intracelular signaling are important. These models can be quickly updated as new results are known and can be a useful instrument for carrying out new work on the basis of the model predictions. Inflammatory cytokine is interleucine 6 (IL-6). The understanding of the signaling mechanisms associated with extracelled IL-6 excitement is important in order to elucidate and modulate biological responses to inflammation. Mathematical models on intracellular pathways are important to understand how cells respond and predict how such stimuli. Such simulations can be easily revised, as new findings are possible and can be useful for new experiments based on the interpretation of the model 's forecasts. In order to clarify and modulate biological response to inflammation, understanding of signal pathways in relation to extracellular IL-6 excitation is essential. Interleucin-6 (IL-6) is the cytokine involved in many inflammatoria processes.

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2.0 Literature review:

Singh, A.; Jayaraman [1] The D-optimality criterion was chosen to minimize the covariance of parameter evaluation on the specified model and to note that no optimal experimental design in any respect ever has a negative effect on the experimental design of other parameters by optimizing one particular criterion.

Huang, Z.; Chu, Y.; Hahn [2] The local sensitivity coefficient represents a shift in a parameter value in the model 's status and is a time and parameter vector function. A sensitivity coefficient for each of the status variables may be determined at some point during an experiment or process simulation.

3.0 Optimal experimental design:

It has been utilized for decades in a variety of settings in which it is of interest to maximize efficiency of resource use and obtain a significant amount of information from experiments with acceptable cost Recently, as biological modeling and systems biology have emerged as an important area in biomedical research, optimal experimental design applied to biological experimental systems has become more popular additionally, optimal experimental design has been recognized as a valuable tool in optimal control for several decades For example, maximized production of an exogenous commodity chemical in metabolically engineered E. coli using an empirical modeling method similar to those used in to maximize the efficacy of drug delivery. utilized optimal experimental design to maximize model prediction accuracy for a model of vesicle transport via the trans-Golgi network. Bandara performed optimal experimental design to reduce parameter uncertainty in a model of phosphatidylinositol trisphosphate signaling. These studies illustrate the efficacy of an optimized laboratory design for extracting the greatest possible knowledge. The problem of optimizing parameter precision for the IL-6 model is simplified by experimental design here. The D-optimality criteria, used in the Fisher Information Matrix (FIM), is particularly maxed through a set of IL-6 concentration input functions to determine an optimum dynamic IL-6 input profile that excits the signaling system to generate the model's less square estimation data..

An ordinary differential equation model, e.g., for describing signal transduction, can be written as

$$\frac{dx}{dt} = f(t,x,u,p);\ y = g(t,x,u,p), \qquad (1)$$

Where x is a time dependent state variable, u is a time-based regulated device entry, p is a constant parameter-vector, and y a model-related variable of calculated quantities. Sometimes, as is the case here, y is just a subset of vector x state variables associated over time. Since such steps are confidential in nature, if the sampling frequency is high enough, the presupposition that y is a constant variable may be created. Information generation tests to be used for the least squares fitting parameter estimate, i.e. vector Y sensitivity coefficients. The FIM is authored

$$\mathbf{F} = \mathbf{S}^{\mathrm{T}}\mathbf{S},$$

where S is the sensitivity matrix

$$\mathbf{S} = \begin{bmatrix} \frac{\partial y_1}{\partial p_1}(t1) & \cdots & \frac{\partial y_1}{\partial p_{np}}(t1) \\ \vdots & & \vdots \\ \frac{\partial y_1}{\partial p_1}(tN) & & \frac{\partial y_1}{\partial p_{np}}(tN) \\ \frac{\partial y_2}{\partial p_1}(t1) & & \frac{\partial y_2}{\partial p_{np}}(t1) \\ \vdots & & \vdots \\ \frac{\partial y_2}{\partial p_1}(tN) & & \frac{\partial y_2}{\partial p_{np}}(tN) \end{bmatrix} \in \mathbb{R}^{(2N)xn_p},$$

The formula shown for S is an experiment in which two state variables from time t1 to tN are measured over the time series; however, for the application studied in this paper, one may extend the formula to any number of test outputs. The local sensitivity coefficients can be calculated by means of a system of common differential equations for all model status variables.

$$\frac{d}{dt}\frac{\partial x}{\partial p^{\mathrm{T}}} = \frac{\partial f}{\partial x^{\mathrm{T}}}\frac{\partial x}{\partial p^{\mathrm{T}}} + \frac{\partial f}{\partial p^{\mathrm{T}}}$$

where x is the column vector of state variables, p is the column vector of model parameters, and f is the column vector of functions defining the model, as in Equation

Optimal Experimental Design Problem for the IL-6 Model

In the IL-6 model, u is the IL-6 concentration induced by IL-6 in the local area. The IL-6 concentration defines at a given time whether the cells signal at a time t defined by each signaling molecule's concentration on the pathway. Therefore, the modulation of the input IL-6 concentration u, as time, will affect signaling dynamics so as to provide the most knowledge about the model parameters to measurement sections of the signal direction, but a constant IL-6 concentration of 100 ng / mL was used for an input function at an arbitrary level for the initial parameter estimate For this analysis, optimal experimental architecture was applied for order to optimize the input function over a continuous series of time-dependent input functions by using a same data collection sequence as was used in this method to determine whether an input function is optimized to minimize the ambiguity of the parameter by keeping other experimental control decisions constant.

$$\begin{aligned} u(t) &= \sum_{k=1}^{r} c_k step(t - (k-1)\Delta t) - \sum_{k=1}^{r} c_k step(t - k\Delta t) \\ &= c_1 \mathrm{step}(t) + \sum_{k=2}^{r} [c_k \mathrm{step}(t - (k-1)\Delta t) - c_{k-1}\mathrm{step}(t - (k-1)\Delta t)] - c_r \mathrm{step}(t - r\Delta t) \\ &= c_1 \mathrm{step}(t) + \sum_{k=2}^{r} (c_k - c_{k-1})\mathrm{step}(t - (k-1)\Delta t) - c_r \mathrm{step}(t - r\Delta t) \end{aligned}$$

where ck is the k-th concentration level in the vector c, 'step' is the Heaviside step function, r is the number of concentration levels in the input function, and $\Delta t = 22$ h/r is the time interval for each concentration level in the input function. By changing the vector c to modulate the IL-6 input function, the solution of the model ODEs and local sensitivity ODEs are modulated.

4.0 Experimental Design for the IL-6 Signaling Model

Solving the optimal experimental design problem for minimizing parameter uncertainty in the IL-6 model for values of r from 1 to 6 resulted in an optimal IL-6 input function for each value of r The range of D-optimality criterion values for the input functions listed in the table (column 4) is very wide if one considers that the values given are the logarithm of the determinant of the FIM rather than the determinant itself.

Table: Optimal and sub-optimal input functions for values of r from 1 to 6.

Input Function (nM)	**r**	Optimal?	D-Optimality Criterion Value	Covariance Norm	Covariance Trace
3.83	1	no	−133.9	161	**216**
6.59	1	yes	−114.5	**43.8**	**45.2**
[0.48, 7.34]	**2**	yes	−28.9	12.95	12.96
[6.30, 1.60, 7.20]	**3**	yes	0.30	0.0033	0.0040
[1.09, 5.22, 0.90, 7.39]	**4**	yes	3.24	6.56×10^{-5}	6.59×10^{-5}
[0.99, 5.64, 0.95, 7.37, 0.97]	**5**	yes	18.8	1.90×10^{-6}	1.91×10^{-6}
[0.89, 5.94, 1.01, 7.14, 1.07, 5.22]	**6**	yes	29.7	4.26×10^{-6}	4.83×10^{-6}
[6.97, 0.67, 7.23, 0.88, 7.49, 1.09]	**6**	no	**19.8**	0.195	**0.204**
[7, 6, 5, 4, 3, 2]	**6**	no	−41.4	**42.2**	**46.8**
[1, 4, 6, 6, 4, 1]	**6**	no	−32.2	**1.63**	**2.03**
[3, 4, 5, 6, 7]	**5**	no	−47.9	**55.5**	**68.8**
[6, 6, 5, 3, 3]	**5**	no	−47.5	**1.32**	**1.44**

Simulations of each of the input functions described in Table For those simulations data were created by the use of the initial IL-6 model and application of the normally distributed noise to the measurements, to test if higher D-optimality criterion values for the input function were compatible with lower uncertainty. In particular, for the basic input function a simulation was performed by integrating the original model IL-6, adding the Gaussian ring with a mean 0 and the normal discrepancy with 1 at the time of measurement (every 45 minutes and 22 hours) and applying to the simulated data the parameters of the condensed model IL-6. However, the relation between the D (a priority calculated) and the (a posteriori defined) uncertainty is not monotonic; e.g., the input uncertainty for r = 5 is somewhat lower than that of r = 6, while the input function for r = 6 is higher (Table). Furthermore, volatility for the function R = 6 is higher, than for the optimal function R = 4 and R = 5, even if the value of the criterion D-optimality for the function R = 6 is higher. There are a number of possible reasons for this lack of monotonicity, such as nonlinearity of the IL-6 model and the fact that optimal experimental design theory is an approximate theory in the case of nonlinear models low, the general shape of the functions is an oscillation between a low and a high value of the input. This suggests that PRBS-like signals may be favorable for minimizing parameter uncertainty in the IL-6 signaling model

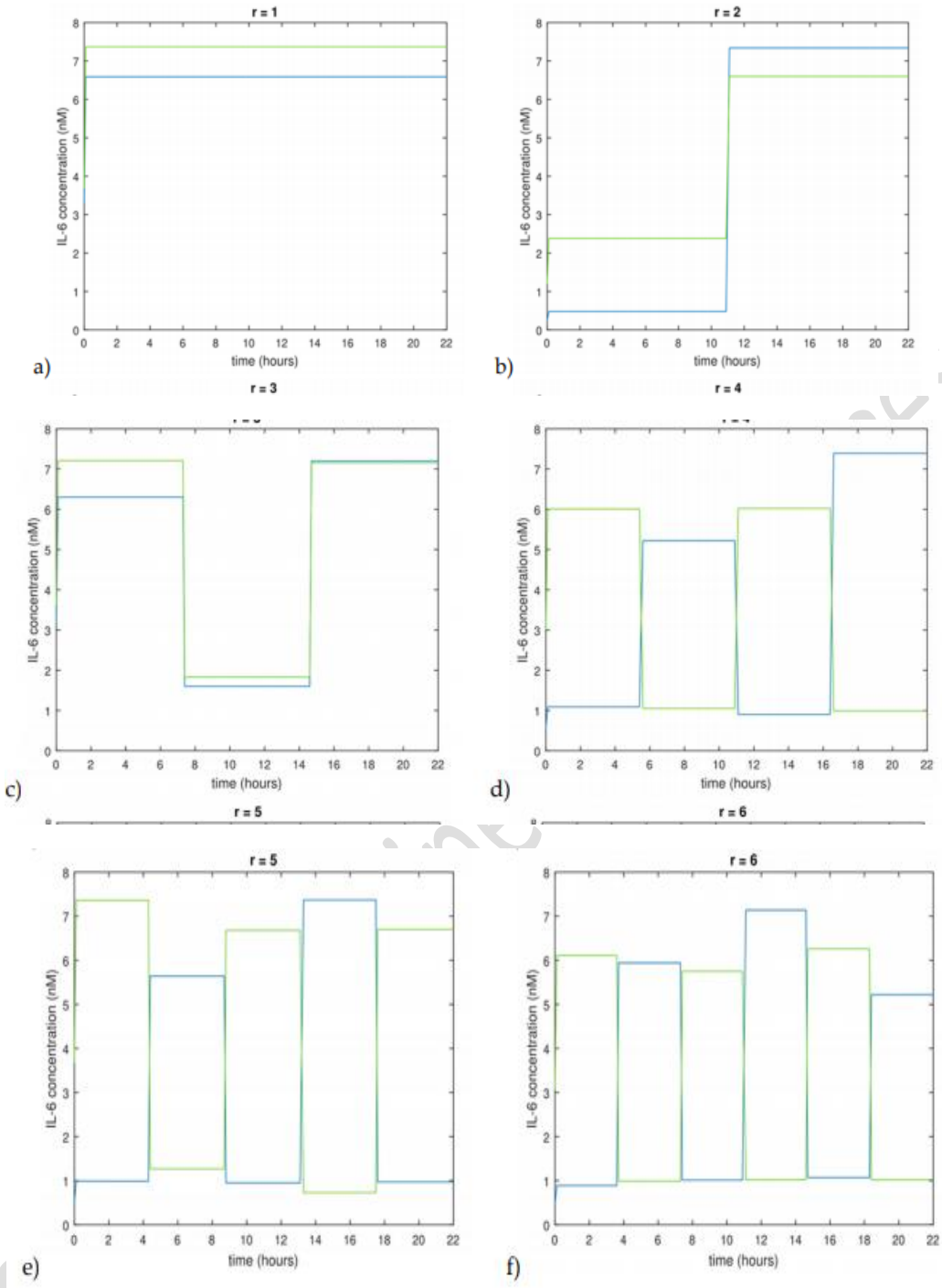

Figure: Optimal input functions for values of r from 1 to 6. Blue indicates input functions identified as optimal from the local sensitivity method; green indicates input functions identified as optimal from the Morris method. (a) r = 1 (b) r = 2 (c) r = 3 (d) r = 4 (e) r = 5 (f) r = 6

Table: Optimal input functions for values of r from 1 to 6 via the Morris method

Vol 11, Issue 6, JUNE /2020
ISSN NO:0377-9254

Input Function (nM)	r
7.37	1
[2.38, 6.60]	2
[7.21, 1.83, 7.15]	3
[6.01, 1.05, 6.02, 0.99]	4
[7.36, 1.27, 6.68, 0.73, 6.70]	5
[6.11, 0.99, 5.75, 1.02, 6.26, 1.02]	6

The main step in the analysis is therefore to calculate all of the partial derivatives in the Jacobian, since the Jacobian will be different for every ODE model. For the Morris method, the information matrix is constructed by sampling from the parameter distribution and calculating finite difference derivative approximations for the sensitivities.

Discussion:

The form of the optimal input functions for the IL-6 model raises an interesting point regarding general system identification theory. Each of the determined optimal input functions takes the form of a PRBS-like sequence a commonly used input signal for system identification even though this input function shape was not postulated during the formulation of the optimal design problem. Furthermore, computing an experimental design where sensitivities were computed via the Morris method also led to PRBS-like optimal inputs. Without commenting on generality, a PRBS signal seems to be a good choice for inputs of the investigated IL-6 signaling model, a result that may potentially carry over to other signaling pathway models.

Conclusions:

Optimal experimental design was applied to the problem of minimizing parameter uncertainty in an IL-6 signaling model representing the Jak-STAT and MAPK pathways. The FIM D-optimality criterion was developed using the sensitivity equations solved with the equations of the model simultaneously. This problem of optimization decided the piecewide constant input functions; the fragmentary complexity of the inputs laid the basis for the implementation on an experimental framework of the defined IL-6 concentration profiles. The optimum input functions contributed to reducing parameter uncertainty of the model; the defined optimal input functions took on the form of PRBS signals from simulations where they were equipped with the optimal input features to trigger the signaling mechanism. Oddly, even though it was not in the best possible experimental design problem. In addition to local methods, the result was further confirmed by the formulation and solution of the problem using a global method. Future research will corroborate these findings by adding an successful trial to the established optimum experimental design.

References:

1. Singh, A.; Jayaraman, A.; Hahn, J. Modeling Regulatory Mechanisms in IL-6 Signal Transduction in Hepatocytes. Biotechnol. Bioeng. 2006, 95, 850–862.

2. Huang, Z.; Chu, Y.; Hahn, J. Model simplification procedure for signal transduction pathway model: An application to IL-6 signaling. Chem. Eng. Sci. 2010, 65, 1964–1975.
3. Chu, Y.; Jayaraman, A.; Hahn, J. Parameter sensitivity analysis of IL-6 signalling pathways. IET Syst. Biol. 2007, 1, 342–352.
4. Moya, C.; Huang, Z.; Cheng, P.; Jayaraman, A.; Hahn, J. Investigation of IL-6 and IL-10 signalling via mathematical modelling. IET Syst. Biol. 2011, 5, 15–26.
5. Himmel, M.E.; Yao, Y.; Orban, P.C.; Steiner, T.S.; Levings, M.K. Regulatory T-cell therapy for inflammatory bowel disease: More questions than answers. Immunology 2012, 136, 115–122. [CrossRef] [PubMed]
6. Eastaff-Leung, N.; Mabarrack, N.; Barbour, A.; Cummins, A.; Barry, S. FOXP3+ regulatory T cells, Th17 effector cells, and cytokine environment in inflammatory bowel disease. J. Clin. Immunol. 2010, 30, 80–89.