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Systems and Control Theory for Medical Systems Biology

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Abstract:

In this chapter the authors describe systems and control theory concepts for systems biology and their corresponding implications for medicine. The context for a systems approach to life science is outlined, followed by a brief history of systems and control theory. The technical aspects of systems and control theory are then described in a way oriented toward their biological and medical application. This description is then used as a reference base against which to indicate specific areas where systems and control theory aspects of systems biology have strong medical implications. Specifically, a set of medically oriented systems biology projects are given as examples of where methods from systems and control theory play an important role.

Keywords: Systems Biology, Systems Theory, Control Systems, Dynamical Systems

INTRODUCTION

In this chapter the authors give their experiences gained working at the interface between the biological/medical sciences, and the physical/engineering systems sciences. In doing so we attempt to convey the powerful contributions that the physical, mathematical and engineering sciences have made, and will continue to make, to innovations in biology and medicine. In this context we stress the role played by systems and control theory in the development of general principles for biological systems, and in particular the understanding of dynamical phenomena in biology and medicine. According to our experiences, systems
methods are influencing the biology research sector through a series of evolutionary scientific steps, as follows:

Stage 1: High-throughput biochemical instrumentation was (and continues to be) developed to provide rapid measurement and generation of data.
Stage 2: To meet the need to process data generated in stage 1, data processing methods were developed to extract information from very large data records.
Stage 3: The information from stage 2 is used to calibrate mathematical models with which to visualise an underlying biological process. This is the current evolutionary state in systems biology.
Stage 4: Control and systems theory are applied to the mathematical models of stage 3 to provide understanding of biological behaviour and underlying principles.

In summary, the sequence goes from:

measurement → data → information → visualisation → understanding.

The current state of the art is that the value of in-silico simulation of biological phenomena is becoming appreciated. Even so, most biological measurement techniques are designed to collect static data, whereas time course data is required to develop mathematical models for visualising system dynamics by in-silico simulation. It is not always appreciated that, as a result of poor data, the calibration and structural correctness of mathematical models is often suspect. Likewise, there is currently little appreciation of the fundamental importance of control and systems theory in understanding biological and physiological phenomena and principles.

On the other hand, the role of systems and control theory is clearly established in the medical community through the understanding that it gives to physiological function. Under the historical influence of Claude Bernard's ideas, as embodied in Cannon's concept of homeostasis (Bayliss, 1966, Cannon, 1932), feedback control is central to many aspects of current medical understanding, although this is usually intuitive and non-theoretical in nature (Tortora, 2003). Since Cannon's work in the 1930's, other researchers have expanded upon the homeostatic feedback principle (Sterling, 2004) in its specific medical and physiological contexts. In the meantime however, systems and control theory has expanded scientifically and progressed to become a mature scientific discipline with fundamental relevance to all areas of scientific endeavour. Through this 70-year period of separate development, the medical concepts of control systems and the mathematical tools of control and systems theory have lost contact. The aim of this article is to reconnect the medical ideas of feedback with mainstream theory by explaining areas where control and systems theory can contribute. We consider this to be vitally important to our scientific futures. For, as indicated above and documented in the recent report Systems Biology: a vision for engineering and medicine (Royal Academy, 2007), the use of systems theory and control concepts will be essential to our understanding of biological systems for medicine.

**BRIEF HISTORY OF CONTROL AND SYSTEMS THEORY**

Control and systems theory have their origins in the 1700's with practical devices designed to regulate speed in wind, water and steam energy sources. In the hurly burly of the Industrial Revolution, design changes to improve the performance of feedback regulators rapidly outstripped their designer's ability to predict their dynamical behaviour. However, as the new invention spread to astronomical instruments, scientists such as Airey and Maxwell
became interested. In this context, the appearance of Maxwell's paper 'On Governors' (Maxwell 1867) was a pivotal point in control and systems theory. It gave a mathematical basis for understanding the stability of physical systems, and made it acceptable for respectable scientists to analyse machines. This process of technical and theoretical development expanded rapidly with industrial growth, covering electrical drives, aircraft, boats and electronic systems. This era is ably described in the historical account (Bennett 1979).

The need for analysis and design methods for electronic amplifiers, just as mechanical regulators before, led to the next crucial development in control and systems theory – the systematic stability analysis and design in the frequency domain. The 1930's framework set by Nyquist (Nyquist, 1932) and Bode (Bode, 1945) for systems and Shannon (Shannon, 1948) for signals informed theoretical developments for twenty five years until the needs of aerospace led to an alternative time-domain (state space) framework of control and systems theory (Bennett, 1993). The 1950’s saw the beginning of a golden age of theoretical and technical advances in control and systems theory. An age during which research became an international endeavour, with theoretical developments emerged rapidly and from numerous independent sources. It resulted in what we have now: control and systems theory as a mature discipline covering: analysis and design of feedback systems, optimal control theory, multivariable systems theory, modelling, systems identification and much more. The following paragraphs will outline these as they relate to systems biology for medicine.

**OUTLINE OF CONTROL AND SYSTEMS THEORY METHODS**

Control and systems theory, together with methods from communication theory, offers a unified structure within which to mathematically represent, analyse, understand and potentially modify the dynamical behaviour of systems and signals. The principle of homeostasis means that control is accept in physiology and medicine (Tortora, 2003), also there are books upon basic control and systems theory in medicine (Riggs, 1976). However in the years between Cannon’s work and now, control and systems theory has developed into a complete theoretical and analytical framework for understanding the behaviour of dynamical systems. In the following we outline the components of this framework.

**Mathematical Models for Control and Systems Analysis**

The primary purpose of mathematical models is to allow the dynamical behaviour of systems to be analysed for design, performance prediction and control (Crandall, 1968). For linear dynamical systems a classical representation of system dynamic is the transfer function model. Such models, developed from the analysis of frequency response systems, have theoretical foundations in Laplace transform methods and complex variables (Smith, 1966). Transfer function methods are not generally used in systems biology applications because they are designed for linear systems. The form of dynamics encountered in biochemical reactions is suited to the alternative form of control and systems model - the state space model (Friedland, 2005).

The state space representation is based upon sets of coupled first order differential equations such as occur naturally in mathematical models of metabolism and signalling pathways. Moreover, the state space form accommodates nonlinear dynamical features such as those that appear routinely in biology/physiology. The control and analysis of state space systems is however only fully developed for the case of linear systems. A range of theoretical methods for stability and performance analysis of nonlinear state space equations exists.
(Freeman and Kokotovic, 1996) and methods especially tuned for state space structures found in life science are in progress (Shelhamer, 2007).

In the following, and unless stated, we will assume that a state space model form is required or used. (Note that hybrid models that combine continuous dynamics (e.g. reaction kinetics) and logical processes (e.g. gene regulation), and/or pure time delays (transport processes) are more complex to analyse.)

Modelling Methods And Computer Based Simulation

The methods for deriving and developing mathematical models of dynamical systems have been thoroughly developed by the control and systems community, (Wellstead, 1979, MacFarlane, 1970). These physical systems methods, suitably augmented by biochemical reaction methods (Cornish-Bowden, 2004), provide a conceptual basis and practical framework for constructing the differential equation/state space models needed to describe dynamical phenomena in biology and physiology. The rapid and easy visualisation of the dynamical behaviour of these models is a basic tool in control and systems analysis and there is a wide range of numerical implementations of dynamical systems simulators for digital computers. A de facto standard for such simulation (and originally developed by control and dynamics experts) is MATLAB (Higham and Higham, 2005). This software has numerous accessories for control and systems analysis. One such accessory is the Systems Biology Toolbox, which is specifically for state space models of signalling and metabolic pathways (Schmidt and Jirstrand, 2006).

The ability to easily visualise the behaviour of a complex dynamical system from its mathematical model has had a particular impact in medicine and physiology (Hunter and Borg, 2003). The multiscale methods needed by such areas however require more general modelling software to allow spatial as well as temporal information to model organ and tissue function (Hunter et. al. 2006). In the same spirit, the simulation of metabolic systems and in particular in-silico pharmacokinetics and pharmacodynamics have profited from dynamical modelling methods founded in systems and control theory.

System Identification and Data Analysis

Writing down the equations of that describes a metabolic process, signalling pathway, gene regulation system or physiological process is only one aspect of mathematical modelling in systems biology. The more demanding aspects are determining (a) whether the model structure is valid (structure identification) or (b) determining the numerical value of the various model parameters (parameter estimation). These two tasks are part of the area known in control and systems theory as system identification. A good view of basic ideas in systems identification is the classic engineering text (Eykhoff, 1974), while statistical time series approaches are covered in an accessible manner elsewhere (Box and Jenkins, 1970). Mathematical based descriptions are given an idiosyncratic and rigorous view in (Ljung, 1987).

System identification is key to creating good models in systems biology in medicine, since it is commonplace for coefficients of models to be unknown, and in many cases the structure of the pathways is uncertain. Indeed some of the most biologically interesting contributions in systems biology have been where system identification has shown that signalling pathway constructed by biological deduction were wrong (Swameye, et. al. 2003). Likewise, the use of parameters from the literature is a poor compromise when they can be directly estimated for the experimental situation in hand.
Identifiability. The degree to which a system can be determined from measured data is termed identifiability (Wellstead, 1975) and it is an important concept. Specifically, in some cases it is impossible to uniquely identify a system uniquely from the available measured data. There are two aspects to this. The first relates to the structure of the system, whereby for certain interrelations in the system it is impossible to unambiguously determine particular parameters or distinguish causality. Feedback structures of the kind found in medical physiology are one such form that gives identifiability problems in distinguishing between forward signal transmission and feedback transmission paths. The further aspect concerns whether the system is sufficiently excited to allow identification from the measured data. This is of particular relevance to medical systems biology where data is often unsuitable for identification. The topic of experiment design is relevant here (Zarrop, 1979).

Random Processes In Control And Systems Theory. Of equal importance to the application of systems identification itself is the thorough analysis and validation of the time course data associated with experimental procedures. All measured data is subject to error (systematic and random) and the correct treatment of such data from dynamical processes is the aim of random data analysis. A comprehensive and practical reference to these methods is (Bendat and Piersol, 2000). The key issue here is that all measurement processes are subject error (systematic and random). Likewise the underlying processes that drive the system may themselves be stochastic in nature and require characterisation with the tools of probabilistic data analysis (Papolis and Pillai, 2002).

Control System Basics

Feedback structures. Control and systems theory gives us a deep understanding of feedback in its practical and theoretical aspects. From the application of feedback in machines, we have developed a complete theory of feedback in linear dynamical systems. This has been mainly applied to designing and building devices that depend upon closed loop feedback control for their performance. In systems biology, the knowledge won in technological development helps us to understand the role of feedback loops in biological processes. In particular, experience of design of technological control systems allows analogies to be found in living systems for such principles as design for regulation against disturbances (c.f. homeostasis), set-point tracking and feedforward compensation. The better understanding of biological, metabolic and physiological function that this affords allows us to predict consequences of interventions that disturb physiological and biological loops. This is particularly true where the system has complex crosstalk between interacting channels in which multi-input, multi-output control system analysis (Skogestad and Postlewaite, 1996) can predict the sometimes unusual responses that occur under feedback conditions.

Stability and Transient Response. The analysis of time course (transient) behaviour is basic to control and systems theory. Its transfer to the understanding of biological dynamics is of paramount value to systems biology in medicine. There are a wide range of theoretical tools in this area, but the most immediately relevant are drawn from state space analysis. They offer insights into the possible convergence points (e.g. steady state) of systems, stability properties and transient performance. Stability analysis of nonlinear systems is particular relevance to systems biology (Slotine, 1991), since all but the most basic of mathematical models of biological systems is nonlinear and with potentially complex dynamical behaviour. Thus stability methods based upon Lyapunov analysis (Bacciotti and Rosier, 2005) and the special structures that occur in life science systems provide insights into behaviour (Angeli and Sontag, 2003).
System Properties

In understanding how to control technological systems, control theorists have formalised a number of mathematical properties that are important to the understanding of systems in general. Key among these properties for systems biology in medicine are observability, controllability, sensitivity and robustness. As follows:

**Observability.** In broad terms, this property relates to the ability to determine states of a system from measurements at the outputs. In systems biology for medicine, the states are concentrations of chemicals in a metabolic, signalling or physiological network. Concentrations that cannot be measured from the available data are said to be unobservable.

**Controllability.** Similarly in broad terms, controllability is the ability of a control mechanism to manipulate all the states of a system from the inputs. This has implications in therapies that aim to adjust biochemical levels by external controls – an uncontrollable state cannot be adjusted in this way. Likewise, in certain signalling pathways it may not be possible from the inputs (e.g. receptor channels) to modify certain chemical concentrations – they are then said to be uncontrollable.

**Sensitivity.** This property is important in the understanding the constraints on performance of a dynamical systems. It relates to the sensitivity of the overall dynamical system to variations in different parts of the system. Thus changes in certain parameters (e.g. kinetic coefficients in a pathway model) may have a big influence on the observable system performance – implying a large sensitivity. Others may have only a small impact – implying insensitivity.

**Robustness.** This property is related to sensitivity, in the sense that one purpose of negative feedback is to make a system robust (that is insensitive) to variations in certain parameters or variables. For example, one purpose of homeostatic loops is to make the metabolism robust against external variations – a side result is that it will be sensitive to others as part of a robustness/sensitivity trade off (Dorato, 1998).

Types of Control System

Related to the properties exhibited by a control system is the purpose that it is intended to serve and the objective or procedure used in its design. Typically, control systems may have the objective that a system variable might be required to follow some external variation within certain limits of accuracy and speed. This would be what is termed classical servo/reference tracking control. Other control systems are set up to maximise (or minimise) some objective function in some optimal way. This is termed optimal control (Bryson and Ho, 1969). When random disturbances predominate then the controller design objective is focussed upon the disturbances. This is termed stochastic control and is treated as branch of optimal control – but more importantly uses Kalman filtering (Kalman and Bucy, 1961). The Kalman/Bucy framework is of huge important to systems biology since it provides a state space framework for understanding and analysing random processes. A further controller type that is relevant to systems biology is coordinating control, where the control mechanism must combine the dual function of regulating local behaviour with coordination, (Mesarovic et al., 2004). Beyond this there are many more specialist control systems that are particular to systems forms and application. The book (Goodwin, Graebe and Salgado, 2001) is modern text that covers almost all of control design methods and types.
EXAMPLES

In this section we give two examples of systems and control theory as they occur in some examples of medical systems biology.

Example 1: The dynamical role of crosstalk between Wnt and ERK pathways in tumorigenesis

In this example, we consider the use of a mathematical state space model of two cell signalling pathways (Wnt and ERK) to investigate their interaction and its implication for cancer studies. Specifically, this is an example of how interaction (or crosstalk) between systems can be studied using systems and control theory tools – specifically state space modelling, simulation and structural analysis to identify hidden feedback loops. The Wnt pathway conveys a signal from Wnt to β-catenin such that the β-catenin level increases by inhibiting GSK-3β, which normally induces the ubiquitination of β-catenin. The increased β-catenin translocates into the nucleus and induces the expression of various oncogenes by forming a complex with TCF (the abnormal increase of β-catenin commonly occurs for colorectal cancers) (Behrens J. 2005). On the other hand, ERK pathway conveys a signal from growth factors such as EGF, PDGF to ERK through the Raf-1 → MEK → ERK cascade. The finally activated ERK (ERKpp) also induces the expression of various proliferation genes (ERK mutants are commonly observed for about 30% of all human cancers).

Figure 1. (A) Crosstalks in the Wnt/ERK pathways and the hidden positive feedback loop formed by these crosstalks. (B) The phase diagrams for a normal status with stimulations over 100 min and 500 min durations, respectively. (C) The phase diagrams for an abnormal status with stimulations over 100 min and 500 min durations, respectively.

The Wnt and ERK signalling pathways are usually considered independent, but there are reports of the crosstalk between them. These include the direct activation of ERK pathway by Wnt, the activation of Raf-1 through unknown molecule X which is induced by β-catenin /TCF complex (Yun, MS et. al. 2005, Rottinger, E. 2004), and the inhibition of GSK-3β by ERKpp (Almeida M, 2005, Ding Q, 2005). If these crosstalks are taken together, then a positive feedback loop is revealed embedded in the Wnt/ERK pathways as illustrated in Fig. 1(A). The systems biology question then arises about the role of this hidden positive feedback loop (Y-K. Kwon, K-H. Cho. 2007, D. Kim. Y-K Kwan, et. al. 2007). In a normal status, the
signalling molecules become activated by external stimulations to respond to environmental changes and then return to their original inactivated states as the stimulation ceases (Fig. 1(B)). However, if there are some mutations and the hidden positive feedback gets enhanced by such mutations (abnormal status), then the system can sustain the activated states even after the external stimulation disappeared (Fig. 1(C)). In other words, the hidden positive feedback loop in the Wnt/ERK pathways can induce an irreversible state change that leads to an oncogenic status.

The state space mathematical model used to produce Fig. 1(B) and (C) is as follows (D. Kim, O. Rath, et. al. 2007):

\[
\begin{align*}
\frac{d[Raf-1]}{dt} &= Wnt + [X] - [Raf-1] \\
\frac{d[MEK]}{dt} &= [Raf-1] - [MEK] \\
\frac{d[ERK]}{dt} &= [MEK] - [ERK] \\
\frac{d[GSK-3\beta]}{dt} &= Const - Wnt - [ERK] - [GSK-3\beta] \\
\frac{d[\beta-catenin]}{dt} &= Const - [GSK-\beta] - [\beta-catenin] \\
\frac{d[\beta-catenin/TCF]}{dt} &= [\beta-catenin] - [\beta-catenin/TCF] \\
\frac{d[X]}{dt} &= [\beta-catenin/TCF] - [X]
\end{align*}
\]

The symbols Raf, Wnt, MEK, ERK, catenin, TCF, etc are system states corresponding to the concentrations of the corresponding proteins in the signalling pathways and the mathematical model was implemented and simulated in MATLAB.

**Example 2: Using a complex systems biology approach to understanding cellular signaling behavior in acute myelogenous leukemia (AML)**

In this example we illustrate a systems framework developed to search for the *coordinating control principles* mentioned previously (Mesarovic et al., 2004). In a multilevel, hierarchical system, the task of a coordinator in the upper level is to harmonize the lower-level subsystems by influencing their functions such that the overall system “goal” is advanced or attained (Sreenath et al., 2007). We demonstrate here a systematic approach to identify a coordinator in a signalling pathway. The identification of a coordinator in a signalling pathway helps in narrowing down molecular targets for further biological study or as biomarkers (for diagnosis). This example examines a conserved pathway, Janus Kinase – Signal Transducer and Activator of Transcription (JAK-STAT), that has been implicated in Acute Myelogenous Leukemia (AML) (Yu & Jove, 2004). The pathway is induced by a small protein, Interleukin-3 (IL3), that effects cell growth and differentiation (Rane & Reddy, 2002). In a healthy cell, IL3 causes transient activation of STAT5 isoform (i.e. STAT5 phosphorylation), whereas in AML, STAT5 is constitutively (continuously) active (Yu & Jove, 2004).

Our beginning point is a mathematical model (including numerical values of nominal parameters) described in (Yamada et al., 2003) that has a different receptor complex, but the same downstream mechanism. To better describe the IL3-induced JAK-STAT5 mechanism,
the receptor complex was modified to be compatible with the IL3 ligand. The biochemical reactions were transformed into nonlinear ODE (Sreenath et al., 2007), resulting in an affine state space model with 49 states, 118 parameters, 2 outputs and IL3 as an input. We estimated 3 receptor complex parameters using semi-quantitative data (Chen et al., 2004) that expresses the relative amount of biochemical in terms of intensity. The biochemical reactions were further modularised using a hybrid method, and represented in the block diagram (Figure 2).

Figure 2. Block diagram representation of the modularized JAK-

A series of in silico experiments were performed to identify a subsystem with the coordinator characteristics (Sreenath et al., 2007). Assuming that each hierarchical system has an overall system objective, a coordinator (at a higher level) should display the following properties: (i) lower level subsystems are functionally independent; (ii) the coordinator can change the lower level subsystems functioning; and (iii) the coordinator can change the lower level subsystem behaviour such that the overall system objective is satisfied. Results show that eliminating the negative regulators – SHP2 or SOCS – causes a behaviour category different from the nominal behaviour (Figure 3). This implies that SHP2 or SOCS modules are candidate coordinators since they are capable of changing the system behaviour. If SHP2 subsystem is a coordinator, the first coordination condition is not satisfied because of the dependency of SOCS on STAT subsystem. To test if SOCS subsystem is indeed a coordinator, a pathological condition was simulated and the parameters varied within the SOCS subsystem until the system was within its nominal behaviour category (Figure 3d). This confirmed the existence of parameters in the SOCS subsystem that promote the overall pathway behaviour to return to normal physiological conditions (Figure 4). Thus, by identifying SOCS subsystem as a coordinator the number of the molecular drug targets has been reduced to twelve from 118 parameters – a factor of ten reduction. The biological verification of SOCS subsystem as a coordinator is the subject of continuing investigation.
CONCLUSION

Systems and control theory concepts have been crucial to the development of technological systems from the Industrial Revolution to date. Indeed, modern day technology depends completely upon theoretical methods of systems and control for its function. The practical evidence is that living systems also use systems and control methods in an organised way to, for example, (a) regulate and organise their performance, (b) achieve certain objectives and (c) resist unwanted external change. Moreover, the systems and control analysis of biological and physiological processes suggests that nature has evolved the methods that are remarkably similar to systems and control theory principles used by engineers in technological applications. This in turn means that we can plausibly hope that systems and control theory analysis can be used in biology and to tease out underlying operational principles that can be of use in medicine. The homeostatic principle is the shining example of such a principle with general application and example 2 in this article presents the essence of another more modern principle.

Figure 3. In silico simulation results. (a) nominal behavior. (b-d) -/- describes a knockdown (elimination) of the indicated biochemical (SHP2 and SOCS respectively).

Figure 4. Illustration of SOCS subsystem (module) as a coordinator, with the JAK-STAT5 system represented as a multilevel hierarchical
References


**Terms and Definitions**

**Closed loop feedback control:** This is the process of continuously measuring the output of a system and using a modified version of the measured output at the systems input so as to alter the overall performance of the system.

**Control theory:** The set of mathematical techniques used to analyse and design control systems.

**Data Analysis:** The analysis of time course data from a system in order to understand the nature of the signal generating mechanisms associated with a system. These are often unwanted noise or errors in the process and are used to modify or correct the mathematical model.

**Dynamical system:** An assembly of components or sequence of reactions whose performance can only be completely described by a study of its behaviour over time.

**Feedback:** The technique of monitoring information from one part of a system and using it to modify a system element at some point prior to the monitoring point. If the monitored information is used to add to the system element it is **positive feedback**, if it is used to subtract from the system element it is **negative feedback**.

**Frequency domain:** The name given to a mathematical space into which mathematical models are transformed for systems and control studies using harmonic analysis of the time course data. This is highly suited for linear systems – in medical systems biology most systems are non-linear.

**In-silico simulation:** The use of a special computer programme to solve the equations of a mathematical model and produce a set of plots of model parameters over time.

**Linearity:** Is the property of a system where if two inputs sequences $X_a$ and $X_b$ produce responses $Y_a$ and $Y_b$, then $X_a+X_b$ will produce the response $Y_a+Y_b$. The system is said to be linear – most biological and medical systems do not satisfy this criteria and are said to be non-linear.

**Mathematical model:** A set of equations, usually ordinary differential equations, the solution of which gives the time course behaviour of a dynamical system. The set of equations for example 1 is an example of a mathematical model.

**MATLAB:** The name of a widely used proprietory software package that is especially suited to the simulation of dynamical system models and their analysis. It is produced by MathWorks Inc. It is adapted from a public domain package of the same name – public domain equivalents are available as Octave and Scilab.
**Pharmacokinetics:** This refers to the dynamical mechanism by which a drug is absorbed, and processed by the body.

**Pharmacodynamics:** This refers to the analysis of the biochemical and physiological effects of drugs and the mechanisms in which they work.

**Stability analysis:** That part of systems and control theory which is used to study and predict the stability or instability characteristics of a system from a knowledge of the mathematical model.

**State Space:** The name given to the mathematical space into which mathematical models are put for systems and control studies using temporal analysis of the time course data. State space (or time domain) analysis is suitable for linear or non-linear systems analysis. This is therefore highly suited to medical and systems biological analysis.

**System Identification:** The analysis of time course data from a system in order to deduce the nature of the system and the values of parameters that could be used in a mathematical model to reproduce the time course data in simulation.

**Systems theory:** The set of mathematical techniques used to analyse and understand the (dynamical) behaviour of systems.

**Transfer function:** The name given to the frequency domain representation of a functional system module with distinct input and output points.