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Modeling and control of high-throughput screening systems in a max-plus algebraic setting ☆

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ABSTRACT

In this paper, we present a max-plus algebraic modeling and control approach for cyclically operated high-throughput screening plants. In previous work an algorithm has been developed to determine the globally optimal solution of the cyclic scheduling problem. The obtained optimal schedule is modeled in a max-plus algebraic framework. The max-plus algebraic model can then be used to generate appropriate control actions to handle unexpected deviations from the predetermined cyclic operation during runtime.

1. Introduction

Until the early 1990s the search for new pharmaceutical ingredients was performed manually. This was an extremely time-consuming procedure lasting for months or even years. Through advances in robotics and high-speed computer technology, it was possible to develop systems that are able to automatically screen thousands of substances in a very short time. The procedure of automatically analyzing biochemical compounds is called *high-throughput screening* (HTS). Nowadays HTS systems play an important role in the pharmaceutical industries, but they are also relevant to other fields of biology and chemistry.

A batch in HTS subsumes all worksteps that are necessary to analyze one set of substances. The set of substances is aggregated on one microplate. Additional microplates may be included in the batch to convey reagents or waste material. The plates are automatically moved between the resources of the HTS system, which include readers, incubators, and pipettors. To be able to compare many different batches of an experiment, each batch has to follow an identical pattern within the system, in terms of timing as well as in terms of ordering of resources. Thus, the system has to be operated cyclically. The aim of maximizing the throughput of the system results in a cyclic scheduling problem. An overview on cyclic scheduling can be found in, e.g., Hanen (1994) and Hanen and Munier (1995).

A method to determine the globally optimal schedules for cyclic systems, such as HTS systems, has been introduced by Mayer and Raisch (2004). This approach is based on *discrete-event systems* modeling, i.e., the system is characterized by the occurrence of discrete changes or events. More specifically, the model is given as a time window precedence network. Using standard graph reduction methods, the complexity of this network can then be reduced. The procedure ensures that the globally optimal solution of the scheduling system is not cut off. Another important step in the proposed method is the transformation of the resulting mixed integer non-linear program (MINLP) into a mixed integer linear program (MILP). Although these steps decrease the complexity of the system significantly, the scheduling problem is still too complex to be performed on-line. Therefore, the algorithm is carried out off-line before the execution of the HTS systems starts, i.e., it determines a static schedule. Static schedules, however, do not perform well when deviations from the predetermined cyclic scheme occur during runtime (Murray and Anderson, 1996).

To handle such deviations, we propose a supervisory control scheme using a *max-plus algebraic* model of the HTS system. The model is based on the specific operation the user wants to run as well as on the globally optimal cyclic schedule determined off-line. In case of a deviation from the cyclic scheme, the supervisor generates possible actions to be taken, i.e., the controller updates the schedule of the HTS plant and thus ensures continuous operation.

This paper is structured as follows. Section 2 summarizes the necessary concepts from graph theory and max-plus algebra. The different constraints for high-throughput screening systems are explained in Section 3. It is described how the constraints are merged into a max-plus algebraic model of the optimal HTS operation. In Section 4, a max-plus algebraic control scheme introduced for cyclic

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systems by Li et al. (2007) is adapted for HTS systems. Conclusions and suggestions for future work are given in Section 5.

2. Graph theory and max-plus algebra

2.1. Graph theory

A directed graph (or digraph) is a pair $(\mathcal{V},\mathcal{E})$, where $\mathcal{V}$ is the set of nodes or vertices, and $\mathcal{E} \subseteq \mathcal{V} \times \mathcal{V}$ is a set of ordered pairs of nodes, called edges or arcs. A weighted graph is a digraph with a real number (the weight) $w_{ji} \in \mathbb{R}$ assigned to each arc $(v_i,v_j) \in \mathcal{E}$. It can be represented by a matrix $W \in \mathbb{R}_{max}^{n\times n}$, with $\mathbb{R}_{max} = \mathbb{R} \cup \{-\infty\}$ and n being the total number of nodes in the graph. The entries of the matrix W represent the weights of arcs. If no arc exists from node v_i to node v_j a weight of $-\infty$ is assigned to w_{ji}. $(\mathcal{V},\mathcal{E})$, together with the weight function $w : \mathcal{E} \to \mathbb{R}$, is then called the precedence graph of W. If the weights $w_{ji} \in \mathbb{R}_{max}$ represent times, the corresponding weighted digraph will also be referred to as a time window precedence network. Then, nodes represent events and arcs represent minimum time offsets between the occurrence of events.

2.2. Max-plus algebra

Max-plus algebra (e.g., Baccelli et al., 2001; Heidergott et al., 2006) is a powerful tool for the analysis and simulation of a certain class of discrete-event systems and provides a compact representation of such systems. It consists of two operations, $\oplus$ and $\otimes$ on the set $\mathbb{R}_{max} = \mathbb{R} \cup \{-\infty\}$. The operations are defined by: $\forall a,b \in \mathbb{R}_{max}$:

$$a \oplus b = \max(a,b),$$

$$a \otimes b = a + b.$$

The operation $\oplus$ is called *addition* of the max-plus algebra, the operation $\otimes$ is called *multiplication* of the max-plus algebra. The neutral element of max-plus addition is $-\infty$, also denoted as ε. The neutral element of multiplication is 0, also denoted as e.

For matrices $A,B \in \mathbb{R}_{max}^{n\times m}$ max-plus addition is defined by

$$[A \oplus B]_{ji} = [A]_{ji} \oplus [B]_{ji}.$$

The matrix product $A \otimes B$ for matrices $A \in \mathbb{R}_{max}^{n\times l}$ and $B \in \mathbb{R}_{max}^{l\times m}$ is defined by

$$[A \otimes B]_{ji} = \bigoplus_{k=1}^{l} ([A]_{jk} \otimes [B]_{ki}) = \max_{k=1,\dots,l} \{[A]_{jk} + [B]_{ki}\}.$$

Similar to conventional algebra, some standard properties, such as associativity and commutativity for $\oplus$ and $\otimes$, and distributivity of $\otimes$ over $\oplus$, hold for the max-plus algebra.

The earliest time instants for the occurrence of events in a timed precedence graph are determined by linear equations in the max-plus algebra. In particular, if we distinguish external (input and output) and internal events,

$$x = A_0 \otimes x \oplus B \otimes u,$$

$$y = C \otimes x,$$

where the vectors x, u and y contain the earliest time instants for the occurrence of the internal, the input and output events, respectively. Note that only the instants of the occurrence of input events, i.e., only the elements in u, can be delayed directly by a controller. The elements of matrix A_0 represent the minimum time offsets between the internal events. If the corresponding graph does not contain any circuits, matrix A_0 is said to be acyclic. In this case the matrix $A_0^* = I \oplus A_0 \oplus A_0^2 \oplus \cdots$ can be determined as $A_0^* = I \oplus A_0 \oplus A_0^2 \oplus \cdots \oplus A_0^{n-1}$, where I is the identity matrix with respect to max-plus algebra. For acyclic system matrices A_0, the implicit representation of the system can be rewritten in an explicit form:

$$x = A_0^* \otimes B \otimes u,$$

$$y = C \otimes x.$$

For cyclically repeated systems, the max-plus model has to be extended such that dependencies of events belonging to different cycles can be included. For systems that are causal with respect to the cycle index, an event in cycle k can only depend on events in the same cycle or in previous cycles. Thus, the recurrence relation for such systems can formally be written as

$$x(k) = \bigoplus_{q \in \mathbb{N}_0} (A_q \otimes x(k-q)) \oplus B \otimes u(k),$$

$$y(k) = C \otimes x(k),$$

with $k \in \mathbb{Z}$. This implicit recurrence relation can be rewritten in explicit form if the matrix A_0 is acyclic:

$$x(k) = \bigoplus_{q} (A_0^* A_q \otimes x(k-q)) \oplus A_0^* B \otimes u(k),$$

$$y(k) = C \otimes x(k),$$

with $k \in \mathbb{Z}$ and $q \in \mathbb{N}$.

2.3. Min-plus algebra

As mentioned in the previous section, max-plus algebra can be used to determine the earliest possible time instants for the occurrences of events in a timed precedence graph. However, it may not always be desirable that an event occurs as early as possible. From a scheduling point of view it is often desired that events occur just in time, i.e., the occurrence of some events shall be delayed as much as possible without interfering with the throughput of the system. The so-called latest necessary event times can be determined with min-plus algebra. Similar to max-plus algebra, min-plus algebra consists of two operations, $\oplus'$ and $\otimes'$ defined on the set $\mathbb{R}_{min} = \mathbb{R} \cup \{+\infty\}$, $\forall a,b \in \mathbb{R}_{min}$:

$$a \oplus' b = \min(a,b),$$

$$a \otimes' b = a + b.$$

The operations are called addition and multiplication of the min-plus algebra. The neutral element of min-plus addition is $\varepsilon' = +\infty$ and the neutral element of multiplication is $e' = 0$.

The standard properties of max-plus algebra, e.g., associativity and commutativity, also hold for min-plus algebra. The matrix operations for min-plus algebra can be directly derived form max-plus algebra by using $\oplus'$, $\otimes'$, ε', and e' instead of $\oplus$, $\otimes$, ε, and e.

3. Max-plus model of HTS systems

An HTS plant is assumed to consist of m resources. According to the operation the user wants to run, the sequence of activities for a single batch is given. It consists of μ activities and each activity i is assigned to one of the resources, denoted by $J_i \in \{1, \dots ,m\}$, where it is executed. During the execution of activity i the respective resource J_i is said to be occupied. Different activities of a batch may overlap in time. Thus, a microplate may occupy two resources at the same time, e.g., during the transfer from one resource to another one. However, we assume all resources to have capacity one, i.e., no activity can allocate a resource while this resource is occupied by another activity.

One possibility to model temporal dependencies between events within a batch is through a time window precedence network. To do this, three different events have to be considered: start events o_i denoting the start of activity i, release events r_i