Max-Plus Algebraic Modeling and Control of High-Throughput Screening Systems with Multi-Capacity Resources

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Abstract: In previous work we have shown how a max-plus algebraic model can be derived for cyclically operated high-throughput screening systems and how such a model can be used to design a controller to handle unexpected deviations from the predetermined cyclic operation during runtime. In this paper, we introduce an extension of this approach for high-throughput screening systems containing multi-capacity resources, i.e., resources that can handle more than one activity at the same time.

Keywords: Cyclic systems, discrete-event systems, max-plus algebra, high-throughput screening, multi-capacity resources

1. INTRODUCTION

High-throughput screening (HTS) has become a standard technology for drug discovery in pharmaceutical industries. HTS plants are fully automated systems that are able to analyze thousands of biochemical compounds in a very short time.

In high-throughput screening, a batch subsumes all worksteps that are necessary to analyze one set of substances. Such a set consists of up to 1536 substances, which are aggregated on one microplate. Additional microplates may be included in the batch to convey reagents or waste material. An HTS plant involves a fixed set of resources performing liquid handling, storage, reading, plate handling and incubation steps. For comparison reasons the sequence and the timing of activities that have to be performed on a batch – the single batch time scheme – has to be identical for all batches. Cyclic operation is therefore an important requirement.

A method to determine 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 at least one globally optimal solution of the scheduling problem is retained. 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 problem significantly, it is still too complex to be solved online. Therefore, the algorithm is carried out offline before the execution of the HTS systems starts, i.e., it determines a static schedule. Static schedules, though, do not perform well when deviations from the predetermined cyclic scheme occur during runtime.

However, using the predetermined static schedule it is possible to develop a max-plus algebraic model of the HTS system's operation (Brunsch and Raisch, 2009). Based on this model, a supervisor may be designed that generates possible actions to be taken in case of unexpected deviations from the cyclic scheme. Doing so, the supervisor updates the schedule of the HTS plant and thus ensures its continuous operation.

In this paper the max-plus algebraic modeling and control scheme is extended to HTS plants containing multi-capacity resources, i.e., resources that can handle more than one activity at the same time. Such resources are contained in many high-throughput screening plants. One of the most common multi-capacity resources in HTS plants is the incubator, where the biochemical substances are allowed to bind to or react (or fail to react) with each other.

This paper is structured as follows. Section 2 briefly describes the fundamentals of graph theory and max-plus algebra. The specifications for high-throughput screening systems are explained in Section 3. Using an illustrative example it is explained how the constraints are merged into a max-plus algebraic model of the HTS operation and how multi-capacity resources can be incorporated into the model. In Section 4, the max-plus algebraic control scheme introduced by Li et al. (2007) is extended to HTS systems with multi-capacity resources. Conclusions and suggestions for future work are given in Section 5.

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2. GRAPH THEORY AND MAX-PLUS ALGEBRA

2.1 Fundamentals of Graph Theory

A directed graph 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 directed graph is a directed graph with a real number (the weight) $w_{ji} \in \mathbb{R}$ assigned to each arc $(v_i, v_j) \in \mathcal{E}$. All weights of the graph can be written as 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. If no arc exists from node v_i to node v_j the corresponding entry in the matrix W is set to $-\infty$. The pair $(\mathcal{V}, \mathcal{E})$ is then called the precedence graph of W. If the weights $w_{ji} \in \mathbb{R}_{max}$ represent times, the respective 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 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: $\forall a, b \in \mathbb{R}_{max}$:

$$\begin{aligned} a \oplus b &:= \max(a, b) \\ a \otimes b &:= a + b. \end{aligned}$$

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.

Addition of matrices in max-plus algebra for $A, B \in \mathbb{R}_{max}^{n\times m}$ is defined by

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

Multiplication of max-plus 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, commutativity, and distributivity of $\otimes$ over $\oplus$ hold for max-plus algebra.

Systems with (cyclic) repetition of events can be represented in max-plus algebra by:

$$\begin{aligned} x(k) &= \bigoplus_q (A_q \otimes x(k-q)) \oplus B \otimes u(k) \\ y(k) &= C \otimes x(k), \end{aligned}$$

with $k \in \mathbb{Z}$ and $q \in \{\mathbb{N} \cup 0\}$, where the vectors $u(k)$ and $y(k)$ contain the earliest time instants for the occurrence of certain input and output events in the k-th cycle. The elements of the matrix A_0 represent the minimum time offsets between events occurring in the same cycle, while the matrices A_q with $q > 0$ refer to minimum time offsets between events in previous cycles and events in the current cycle. If matrix A_0 is acyclic, i.e., its precedence graph does not contain any circuits, the matrix $A_0^* = I \oplus A_0 \oplus A_0^2 \oplus \dots$ can be determined as the finite sum $A_0^* = I \oplus A_0 \oplus A_0^2 \oplus \dots \oplus A_0^{n-1}$, where I is the identity matrix with respect to max-plus algebra. In this case the implicit recurrence relation can be rewritten in an explicit form:

$$\begin{aligned} x(k) &= \bigoplus_q (A_0^* \otimes A_q \otimes x(k-q)) \oplus A_0^* \otimes B \otimes u(k) \\ y(k) &= C \otimes x(k), \end{aligned}$$

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

3. MAX-PLUS MODEL OF HTS SYSTEMS

The specific operation the user wants to run determines requirements for the single batch time scheme. It consists of i_{max} activities which are executed on m resources. Thus, each activity i is assigned to a specific resource $J_i \in \{1, \dots, m\}$. During the execution of activity i the respective resource J_i is said to be occupied. As activities of a batch may overlap in time, it is possible that a batch occupies two resources at the same time. This is, for example, the case during transfer of a microplate from one resource to another one.

The minimal requirements for the single batch time scheme can be modeled using time window precedence networks. To do so, each activity i is described by three different kinds of events, i.e., start events denoted by o_i, release events denoted by r_i, and transfer events. The time window precedence network of a simple example is given in Fig. 1.

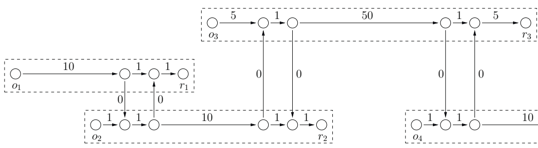

Fig. 1. Time window precedence network to describe requirements for a single batch time scheme.

Often scheduling problems are illustrated by Gantt charts. The Gantt chart of our example is given in Fig. 2. It can be seen that the operation contains four activities, which are executed on a total of three resources. While *Reader* and *Pipettor* are single-capacity resources, *Incubator* is of capacity three. That means that the resource *Incubator*

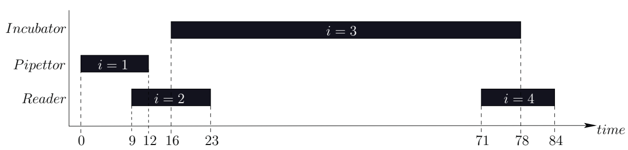

Fig. 2. Gantt chart of the single batch time scheme

can mount a total of three microplates at the same time. Usually *Incubators* are of a much higher capacity. For simplicity and illustrative reasons, however, we will assume the rather small capacity of three in our running example.

In general, a multi-capacity resource with capacity $cap = \xi$ can handle ξ activities concurrently. These concurrent operations are executed independently from one another.