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Sample Testing with Vitalab Flexor

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Abstract

The Vitalab Flexor is a high-tech medical instrument designed to perform a large number of simultaneous measurements on samples of blood and urine. For future purposes it is desired to increase the throughput, i.e. the number of tests per hour, of the instrument.

The analysis in this report gives upper bounds on the throughput if the Vitalab Flexor is operated in modes which are standard in the present situation. It is shown that a desired throughput of at least 266 tests per hour can not be realized on the basis of these standard operation modes. Possible improvements are suggested via so-called parallel or on-line operation modes, or a combination of these two modes. These possible improvements however require a number of changes in the technical design of the Vitalab Flexor.

Keywords

Sample testing, throughput, bounds.

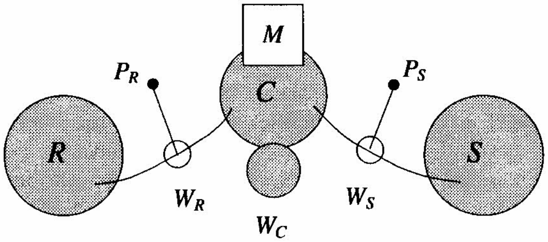
2.1 Introduction: the company, the instrument and the problem

AVL Medical Instruments is a group of technology-driven companies operating world-wide in critical care analysis, since its formation in 1967. Currently some 1700 specialists in more than 90 countries are active in developing and selling products and services in all five continents. One such product is the Vitalab Flexor for testing samples for medical purposes, e.g. blood and urine. The main parts of the Vitalab Flexor are three rotors.

- The *reagent rotor* is able to hold 24 reagents (such as glucose and cholesterol) in 25 ml. bottles and 8 reagents in 5 ml. bottles. With the help of adaptors 5 ml. bottles can also be placed in 25 ml. positions.
- The *reaction* or *cuvette rotor* has a capacity for 48 cuvettes. It is kept at a temperature of 37°C. Minimum measuring volume is 220 μl. Cuvettes are cleaned and dried before use.
- Each position in the *sample rotor* can contain a 5 ml. primary tube (sample cup). The sample rotor contains an outer segment for 48 samples and/or calibrators, and an inner segment for various purposes (fluids).

Measurements take place in the reaction rotor, after samples and reagents have been brought together from the sample and reagent rotor into the pipettes. This is done with the help of a sample and a reagent pipettor. Six wash stations take care of the washing and drying of cuvettes and pipettors after each measurement. The wash station for cuvettes is also provided with a device that prevents the system in the reaction rotor from flooding.

A schematic picture of the complete Flexor system in shown in Figure 2.1.



M: Measurement Station

P_R: Reagent pipettor, P_S: Sample pipettor

R:	Reagent rotor	C:	Cuvette rotor	S:	Sample rotor
W_R:	Wash station for reagent pipettor	W_C:	Wash station for cuvettes	W_S:	Wash station for sample pipettor

Figure 2.1: The apparatus

The process of sample testing consists of three major steps.

Step 1: Mix sample and reagent in a cuvette following some protocol that prescribes the amounts of fluid and the timing of consecutive actions.

Step 2: Measure the absorbance of the mixture at different wavelengths.

Step 3: Clean cuvette and pipettors. Cleaning is done without the use of disposables and without cross-contamination.

There are three types of test protocols:

- **End point tests (single reagent mode)**
  For these test protocols first a reagent and afterwards a sample is added to the cuvette. Measurement takes place once between adding the reagent and the sample and once some fixed time after adding the sample.
- **Kinetic tests (single reagent mode)**
  These tests are similar to the end point tests. The only difference is that after adding the sample not one but a series of measurements take place. Between the latter measurements the intermediate time distance is constant.
- **Dual reagent mode tests**
  For these tests after adding a first reagent and the sample a second reagent is added. Between adding the sample and the second reagent a fixed time has to pass. Measurement takes place once between adding the first reagent and the sample, once shortly before adding the second reagent, and several times after adding the second reagent. Again, the intermediate time distance between the latter measurements is constant.

In an advertisement folder the company mentions that the maximum throughput of the apparatus is 133 tests per hour if all test are dual reagent mode tests. Measurements, including filling and mixing (called washing), in a dual reagent sample test take about 11.5 minutes, in a mono reagent test sometimes about 11.5 minutes as well, but more often (in 80% of all cases) only 4.5 minutes. A single measurement lasts for 0.5 seconds in total, i.e. including starting and stopping of the cuvette rotor. The numbers of single and dual reagent tests in a real life situation are more or less equal.

More detailed information on the Vitalab Flexor will be presented in Section 2.2 in connection with a discussion on global performance measures for the apparatus.

The two main questions to be discussed are:

1. What is the maximal throughput of the current version of the Vitalab Flexor?
2. What changes can be made in the apparatus to increase the throughput (current goal: 266 tests/hour in dual reagent mode).

To find an answer to these questions it is necessary to gain more insight into the sensitivity of the system (apparatus) for certain parameters. The analysis, described in Section 2.3, leads to a number of observations regarding the throughput of the system and suggestions for possible improvements. For example, as an alternative to measuring in cyclic operation mode one could think of random access in future designs.

2.2 Analysis of the Vitalab Flexor

In this section we will discuss the influence of several parameters of the system (Vitalab Flexor) on the throughput. To be able to do this we first will present some more details of the system and the structure of the tests. Afterwards, we will consider two special operating modes for the system and derive upper bounds on the throughput for these operating modes.

2.2.1 The sample rotor and test actions

As mentioned in the introduction, the Vitalab Flexor consists of three rotors. However, the reagent rotor and the sample rotor have almost no direct influence on the throughput. They only have to be designed such that enough reagents and samples are provided to the system. The cuvette rotor is more crucial since its size determines how many tests can be performed in parallel within the system. Therefore, we will consider the number n_{cu} of cuvettes in the cuvette rotor as one of the parameters of the system (in the current version of the Vitalab Flexor we have $n_{\text{cu}} = 48$).

Besides the number of tests which can be stored in the cuvette rotor (=number of cuvettes) also the times needed to perform the different actions (measure, add reagent, add sample, wash cuvette) for these tests form a limitation. These times are estimated as follows:

measurement (M)	0.5 seconds
add first reagent (R1)	1.5 seconds
add second reagent (R2)	5 seconds
add sample (S)	5 seconds
washing (W)	2 seconds

- R2 and S include the time for mixing the added fluid with the fluid already in the cuvette (therefore, R2 needs more time than R1). The mixing is done with the needle of the pipettor.

- The reagent (sample) pipettor can fill only at one position of the cuvette rotor.

- Between two consecutive actions of a pipettor, it has to be cleaned in the corresponding wash station. Currently, this lasts approximately 8 seconds. As a consequence, the minimal time distance between two consecutive actions of a pipettor is also 8 seconds.

- At the end of a test the cuvette containing the test fluid has to be cleaned. This is done in 6 steps each taking 2 seconds. Between consecutive steps there has to be some time distance (currently 27 seconds). This distance, however, is not sensitive (i.e. also smaller or larger distances are possible). In Step 1 the fluid of the test is suck out of the cuvette and a washing lotion is syringed into it, in steps 2 to 4 the current washing lotion is replaced by a new, in Step 5 the last washing lotion is suck out, and in Step 6 the cuvette is dried. Each time the system does a washing action it processes all 6 steps in parallel for 6 neighboring cuvettes (see Figure 2.2). Thus, if one wants to start washing a certain cuvette, one has to make sure that several neighboring cuvettes are empty or contain test fluids for which already all measurements are finished.

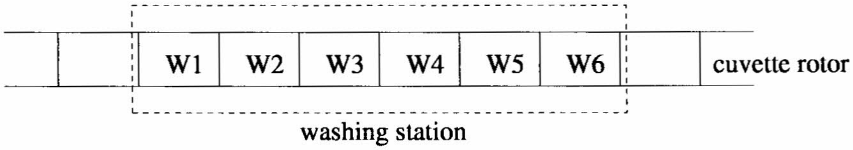


Figure 2.2: Design of the washing station

2.2.2 Test protocols

Next, we will give some more information on the test protocols. All three protocols first fill the cuvette with the first reagent (R1), then measure once (M), and next add the sample (S). The time distances between these actions are not sensitive. For the end point test additionally only one measurement takes place approximately 4.5 or 11.5 minutes after S. For the kinetic test additional 10 or 21 measurements take place with an intermediate distance of 27 seconds between two consecutive measurements. For the dual reagent tests approximately 4.5 minutes after S a second reagent (R2) is added. Shortly before this second reagent is added a measurement takes place. After R2 another 11 measurements are performed. As for the kinetic test the intermediate distance between these measurements is 27 seconds. Figure 2.3 gives a summary of the actions for the different types of tests. The general pattern on top of the figure is a union of all the actions which may have to take place in the tests. Thus, if all actions of the general pattern are performed for some test (allowing 'empty' action; i.e. R2 adds no reagent or the data of a measurement M are ignored) we are sure that the test is treated correctly, independently of the type.

Based on the structure of the tests, there are two principle modes to operate the system.

- cyclic operating mode
  In this mode a fixed work pattern for the cuvette rotor (sequence of actions) is defined for a fixed time interval and this work pattern is performed iteratively. In each iteration the actions are performed on different cuvettes.

- on-line operating mode
  In this mode an arbitrary order of actions can be performed for the cuvette

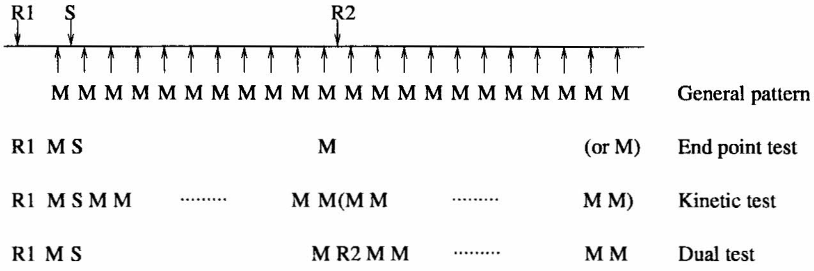


Figure 2.3: Structure of the tests

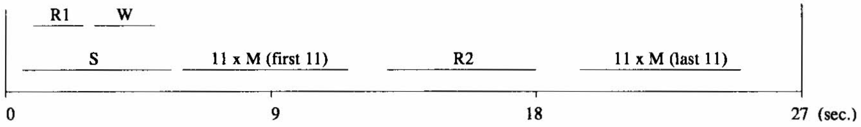


Figure 2.4: Work pattern of the current system

> rotor. As a consequence, it is possible to treat all tests individually and to determine a schedule for the cuvette rotor based on the type of tests to be performed. This implies that for the on-line operating mode an algorithm has to be designed which calculates a feasible schedule on the cuvette rotor maximizing the throughput of the system on the base of the tests added into the system.

In the following subsection we will discuss the cyclic operating mode (which is the operating mode of the current version of the Vitalab Flexor) in more detail. The on-line operating mode will be discussed in Subsection 2.2.4.

2.2.3 Cyclic operating mode

A solution for the cyclic operating mode is specified by the cycle time t and a work pattern for a time period $[0, t]$. Since this work pattern is repeated iteratively independent of the types of tests which have to be executed, we have to perform for each test the general pattern defined in Figure 2.3. Depending on the type of a test some of the actions will be 'empty'. Furthermore, the cyclic structure of the schedule implies that in one time period $[0, t]$ the actions belonging to k general patterns, $k \in \mathbb{N}$, have to be carried on. The current cycle time is defined as $t = 27$ seconds and the current work pattern is given in Figure 2.4. In this work pattern the actions of one general pattern are executed. As can be seen from the figure, some actions may occur in parallel (e.g. during the time in which the sample is added to a cuvette, the first reagent is added to another cuvette and the washing station applies washing steps to 6 cuvettes). However, since during such a period the cuvette rotor does not move and since all actions can be executed only at fixed positions, the distance between the positions of the cuvettes where actions are executed in parallel is fixed. Furthermore, notice that R1 and R2 are separated always by more than 8 seconds (time needed to clean the reagent pipettor).

In the current system the work pattern from Figure 2.4 is iterated in such a way that if in iteration i an action is executed for cuvette j it will be executed for cuvette $j+1$ in iteration $i+1$. This ensures that the distance between two consecutive measurements of the same test is 27.5 seconds (only between the 11th and the 12th measurement the distance is larger, however, the distance between these two measurements is not sensitive).

In the following we will derive some upper bounds on the throughput of the system in a cyclic operating mode. The first bounds are achieved by considering the work load of the cuvette rotor and the second by considering the number of cuvettes.

Upper bounds via work load

First, note that in the cyclic operating mode only cycle times which are a multiple of 27 seconds make sense (restriction on the time distance between consecutive measurements). Thus, we may restrict ourselves to $t = n \times 27$ seconds, $n \in \mathbb{N}$. Assume, that k tests (actions of k general patterns) are executed in one work pattern. This implies that k times the actions R1, R2, S, and W and $22k$ times the action M have to be executed within the time interval $[0, t]$. Since R1 and R2 can not be done in parallel and since during each execution of R1 and R2 only one measurement can take place (only one cuvette is in front of the measurement station), we need at least

$$k \times |R1| + k \times |R2| + k \times (22-2) \times |M| = 16.5 \times k$$

seconds to execute all k general patterns. Since t is an upper bound on this time we get

$$16.5 \times k \leq t = n \times 27 \Longleftrightarrow k \leq \frac{54}{33} n \approx 1.64n.$$

For $n = 1$ (which in practice is a preferable situation since it is easy to implement and to handle) this yields $k \leq 1.64$ and since $k \in \mathbb{N}$ we get $k \leq 1$. As a consequence the throughput of the system in this case is limited by

$$\frac{1 \text{ test}}{27 \text{ seconds}} \leq 133 \text{ tests/hour}.$$

For arbitrary values of n we get a bound of

$$\frac{\frac{54}{33} \text{ tests}}{27 \text{ seconds}} \leq 1.64 \times 133 \text{ tests/hour} = 218 \text{ tests/hour}.$$

These bounds rely only on the work load of the cuvette rotor and, thus, are independent of the number n_{cu} of cuvettes on the rotor. As a consequence, a throughput larger than the above values can only be achieved if the processing times of some of the actions are reduced or more actions can be executed in parallel.

The bound for the case $n = 1$ is realistic (based on rounding down the value 1.64 to 1) and can be achieved if enough cuvettes are available to store the tests. However, the general bound of 218 tests/hour is too optimistic. On the one hand we have ignored that between different actions the cuvette rotor has to move to another position which will take some time. On the other hand, we have assumed that several actions are executed in parallel (S, W, and one M parallel to R2 and one M parallel to R1) which may cause difficulties since parallel actions have to be executed for cuvettes with a fixed distance. Thus, even if enough cuvettes are available and long cycle times (larger values of n) are used, the real throughput of the system will be below 218 tests/hour. In Figure 2.5 the dependency of the throughput of the system on the time needed for a single test (t_{test}) is given.

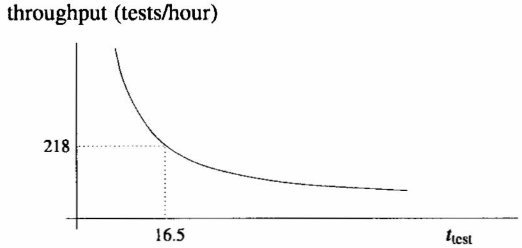


Figure 2.5: Relation between throughput and time needed for a single test

Upper bounds via number of cuvettes

Since in a cyclic operating mode each test has to be processed according to the general pattern given in Figure 2.3, each test will occupy a cuvette for at least the time T it needs to traverse this general pattern. A lower bound on T is given by the time it needs to perform the 22 measurements ($\geq 21 \times 27$ seconds) plus the time for the 6 steps for washing the cuvettes (6×2 seconds for the steps plus 5×10 seconds as minimal waiting time between two steps); i.e. $T \geq 629$ seconds. Thus, each cuvette can perform at most

$$3600/629 = 5.72 \text{ tests/hour.}$$

If one restricts the cyclic operating mode to a cycle time of $t = 27$ seconds, the minimal time needed to traverse the general pattern will grow to 27 times the cycle time since all 22 measurements and all 6 washing steps have to be executed in different cycles (the last measurement and the first washing step may be in the same cycle).

This yields $T \geq 729$ and a bound of at most

$$3600/729 = 4.94 \text{ tests/hour}$$

for each cuvette.

The above bounds on the throughput for each cuvette results for the system with 48 cuvettes in a throughput of at most $5.72 \times 48 = 274$ tests/hour for the general case and of at most $4.94 \times 48 = 237$ tests/hour for a cycle time of 27 seconds. These bounds rely only on the assumption that a cyclic operating mode is chosen and 48 cuvettes are on the rotor. Thus, even if the processing times of all actions are almost 0 and all actions can be executed in parallel the throughput of a system with 48 cuvettes can not be above these values in the cyclic operating mode. Let n_{cuvettes} be the number of cuvettes (= 48 in the present situation). Then throughput depends linearly on n_{cuvettes} in a way shown in Figure 2.6.

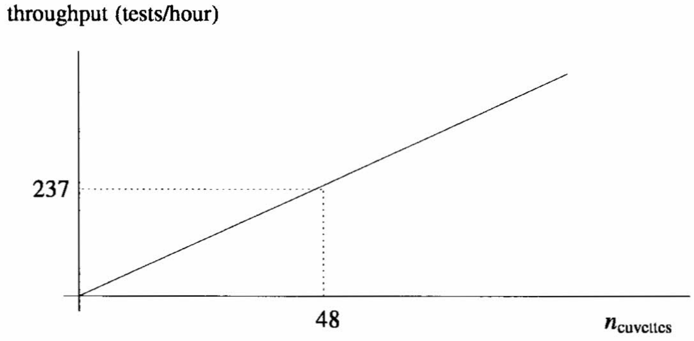


Figure 2.6: Relation between throughput and number of cuvettes

2.2.4 On-line operating mode

The main drawback of the cyclic operating mode is that one executes all tests according to the general pattern given in Figure 2.3 and, thus, 'empty' actions are scheduled. Furthermore, the end point tests and the kinetic tests may occupy a cuvette much longer than needed. To overcome these disadvantages, one has to switch to an on-line operating mode. Here a schedule has to be calculated on the basis of the real types of the tests to be performed. This implies that a scheduling algorithm has to be designed which calculates a feasible schedule for the cuvette rotor maximizing the throughput of the system on the basis of the tests added into the system. The difficulties arising in this context will be discussed in the following section. In the remainder of this section we will calculate upper bounds on the throughput which may be achieved by switching to the on-line operating mode.

Bounds on the throughput of the system will depend on the distribution of the types of tests to be performed. In our calculation we use a typical distribution given by AVL (only kinetic and dual tests):

dual tests	50%
short kinetic tests (11 measurements)	40%
long kinetic tests (22 measurements)	10%

To calculate an upper bound on the throughput on the basis of the work load, assume that this throughput is p tests/hour. Thus, in an hour the cuvette rotor has to process on the average p times R1, S, W, $0.5p$ times R2, and $(0.5 \times 13 + 0.4 \times 11 + 0.1 \times 22)p = 13.1p$ times M. Half of the times S is executed one could do in parallel one R2, W, and M. During the other executions of S one could do in parallel one R1, W, and M. Parallel to the remaining $p/2$ executions of R1 one measurement may take place. Thus, a lower bound on the work load of the cuvette rotor is given by:

$$p \times 5 + p/2 \times 1.5 + (13.1 - 1.5)p \times 0.5 = 11.55p \text{ seconds}$$

This yields an upper bound of $3600/11.55 = 311$ tests/hour independently on the number of cuvettes on the rotor.

For the on-line operating mode the bounds on the base of the number of cuvettes are not so effective. As mentioned in the previous subsection the dual tests and the long kinetic tests occupy a cuvette for at least 629 seconds. In the same way a lower bound of 332 seconds results for the short kinetic tests. This yields that a test occupies a cuvette on average for 510 seconds and, thus, each cuvette can execute on average 7.06 tests/hour resulting in an upper bound of 388 tests/hour for a system with 48 cuvettes independently of the processing times of the actions.

Both calculated bounds are less realistic than for the cyclic operating mode since in the above calculations the restriction that consecutive measurements of the same test have to be executed with a time distance of 27 seconds are relaxed as well as the restrictions resulting from the layout of the washing station.

2.3 Possible modifications

In this section we will discuss the influence of two possible modifications of the system. In the first subsection we will investigate the influence of parallel measurement and in the second the problems arising from using an on-line operating mode.

2.3.1 Parallel measurement

The goal of AVL is to design a system with a throughput of at least 266 tests/hour. Furthermore, from a practical point of view it would be preferable to proceed in a cyclic operating mode with short cycle times (if possible with 27 seconds). However, the discussion in Subsection 2.2.3 has shown that for such a setting a throughput of 266 tests/hour is not reachable. To be able to enlarge the throughput

- the work load of the cuvette rotor for one general pattern has to be reduced
- the number of cuvettes on the rotor has to be enlarged.

Since the 22 measurements contribute significantly to the work load, one possible modification (which is possible in practice) is to do all measurements in parallel. More precisely, the measurements are done by rotating the cuvette rotor one complete round and measuring 'on flight' the contents of all cuvettes. The time needed for measuring all the cuvettes in this way is approximately 3 seconds. Thus, in a cycle of 27 seconds 24 seconds remain for the remaining actions. The remaining work load on the cuvette rotor for k general patterns can be estimated from below by (see Subsection 2.2.3)

$$k \times |R1| + k \times |R2| = 6.5 \times k.$$

Thus, we get $k \leq 24/6.5 \approx 3.7$. Since $k \in \mathbb{N}$ this results in a bound of at most 3 general patterns for a cycle time of 27 seconds if the measurements are done in parallel.

Performing k general patterns in a cycle of 27 seconds will result in a throughput of the system of $k \times 133$ tests/hour. However, to be able to achieve such a throughput, several other constraints have to be taken into account:

- R2, S, and W always have to be scheduled in parallel.
- At least $k \times 27$ cuvettes are needed, since each test will occupy the cuvette for at least 27 cycles (22 measurements, 6 washing steps, last measurement and first washing step may be done in the same cycle).
- The sample rotor and pipettor have to handle k samples in 24 seconds.
- The reagent rotor and pipettor have to handle $2k$ reagents in 24 seconds.

Whereas, the first condition depends on the possibility to find a feasible work pattern for a cycle of 27 seconds, the last three conditions ask for technical changes of the current system.

In the remaining of this subsection we will briefly discuss the difficulties and possibility to realize a solution with $k = 2$. The most crucial obstacle seems to be the condition to perform 2 times R1 and R2 in 24 seconds. This condition asks for a drastic reduction of processing times used in the current version of the Vitalab Flexor (the four tasks R1, R1, R2, and R2 and the 4 washing processes together take 37 seconds). If these reductions are not possible or only possible by using expensive techniques, an alternative could be to use two reagent rotors each with an own pipettor or one reagent rotor with two pipettors. The restriction on the sample rotor seems to be less problematical, since a small reduction of the washing time and/or the S will be sufficient to perform 2 times S within 24 seconds. Finally, a larger cuvette rotor has to be designed to implement a solution with $k = 2$. Note however that 54 cuvettes is only a lower bound on the size of the cuvette rotor, which results from the assumption that a general pattern needs at least 27 cycles to be performed. The number which really has to be implemented depends on the number of cycles which it takes in a concrete feasible schedule for processing one general pattern.

2.3.2 On-line operating mode

As calculated in Section 2.2.4 an upper bound on the throughput for the on-line operating mode is given by 311 tests/hour. This bound relies on the assumption that the cuvette rotor is always busy and that a lot of actions are performed in parallel. However a closer look at the restrictions for a feasible schedule show that these assumptions are far from practice:

- if for a kinetic test the first measurement or for a dual test the measurement directly before R2 have been scheduled, the following 11 (or 21) measurements for the corresponding test have to be scheduled exactly 27 seconds later. Furthermore, in a dual test scheduling S implies an almost fixed time for the processing of the corresponding R2 action. Thus, after fixing a few actions the future time horizon will contain a lot of 'blocked' time periods resulting in less freedom to schedule further action. As a consequence, a realistic schedule surely will contain a lot of idle times on the cuvette rotor.

- actions on the cuvette rotor can only be processed in parallel if the cuvettes to which these actions have to be applied have a fixed distance. However, to fully use the on-line operating mode after some operating time, this condition hardly will be fulfilled and, thus, only very seldomly actions may be performed parallel (at least as long as a realistic number of cuvettes is used).

The above two points indicate that the given bound of 311 tests/hour is much too optimistic and that it in practice seems to be also very unlikely that the current version of the Vitalab Flexor can achieve a throughput close to the desired 266 tests/hour if the operating mode is changed to an on-line mode.

However, in combination with a parallel measurement the situation changes. Since all measurements are done in an time interval of 3 seconds, and these intervals occur all 27 seconds, the timing restrictions of the measurements are always fulfilled. The only restriction on the further schedule is that each 27 seconds already an interval of 3 seconds is blocked for further actions. For scheduling these remaining actions mainly minimal time delays have to be taken into account:

- R2 → S ↔ R2 → W
  (→ indicates a minimal time delay and ↔ a fixed time delay between the actions)
- R' → R"
  (R' and R" denote different R1 or R2 actions)
- S' → S"

These are much simpler restrictions on the schedule than for the case of individual measuring. However, as mentioned in the previous subsection the parallel measurement implies some further changes to the system.

2.4 Concluding Remarks

The aim to realize a throughput of at least 266 tests/hour for the Vitalab Flexor has been shown to be unrealistic for the current design in combination with the (as yet standard) cyclic operation mode. The weakest upper bound seems to allow a throughput of 274 tests/hour, imposed on the system by the limited number of 48 cuvettes. This figure however is far too optimistic since, among other neglected factors, it does not account for finite cycle times, nor for the work load generated by the different actions in a test. Considering the bounds resulting from the work load of the cuvette rotor in the cyclic operation mode with an identical work pattern for all three types of tests, which is common practice, the most optimistic but least realistic estimate gives a throughput of 218 tests/hour.

Throughput can be increased by a more efficient use of the current system and by technical improvements, possibly in combination. Regarding the operation of the system one could think of parallel measurements for a number of simultaneous tests. This can be achieved by measuring the contents of all occupied cuvettes during one complete round of the rotor. For a number of k tests which are measured in parallel, an upper bound of $k \times 133$ tests/hour on the throughput results, but only if some technical changes are applied to the current system. However, for a value of $k = 2$ already such changes imply drastic reductions of processing times for various actions in a test.

As an alternative to the cyclic operation mode a so-called on-line mode results in an upper bound of 311 tests/hour. In this mode the identical work pattern for the three different types of tests is replaced by an approach in which feasible schedules are calculated for the cuvette rotor on the basis of the real types of the tests. The upper bound of 311 tests/hour for an arbitrary number of cuvettes in the rotor is much too optimistic on its turn, since it does not include all kinds of incompatibilities in the system. For example the bound is calculated as if actions in different tests can be performed in parallel, requiring a fixed distance between the cuvettes to which the actions are applied. In practice this condition will very seldomly be fulfilled.