Development of a module for an automated diagnostic system for antibodies G and M

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Abstract. The infectious disease COVID-19 occurs as a result of infection with the SARS-CoV-2 coronavirus strain. Most often, COVID-19 proceeds with signs of an acute respiratory viral infection (ARVI) (fever, cough, body aches); loss of smell, nausea, and shortness of breath are possible. However, in a large percentage of those infected, the course of the disease is asymptomatic. After the virus entry into the body, the immune system begins to produce antibodies specific to this virus (IgM - immunoglobulins) - an important factor in the formation of the immune system's defense against infection. Antibody testing is recommended as an additional method for diagnosing an acute infection or when it is impossible to study smears by amplification of nucleic acids, to identify individuals with an asymptomatic form of infection, to establish the fact of a previous infection, and also to select potential donors of immunocompetent plasma. Determination of antibodies of different classes in the blood is informative evidence of the current or past infectious process and helps to identify the stage of the infection development. More often, the level of antibodies of class M (IgM) and G (IgG) is determined in the blood. The development of the instrument base of express analyzers for monitoring the presence of antibodies to the new coronavirus infection COVID-19 is currently relevant in connection with the emerging and ongoing pandemic. It is possible to use the following systems as test analyzers for immune enzyme medium: ARCHITECT – IgG, Abbott and ELISA-IgM-BEST. For the hardware, an Omron industrial controller and CX-One programming system can be used. The truth table for the formation of signals on the diagnosis of the disease has been developed to obtain logical equations for the operation of the analyzer module. The synthesis of relay-contact circuits has been carried out. The simulation of the module's operation showed satisfactory results. Timely and correct diagnostic measures make it possible to diagnose and assess the severity of the disease as early as possible.

1. Introduction
During the pandemic of a new coronavirus infection (COVID-19), 80% of patients have an asymptomatic or mild disease. In the spring-winter period of 2021, the third wave of COVID-19 is expected. To protect the body in February-March 2021, it is planned to vaccinate the population, but,
nevertheless, the development and availability of express analyzers for COVID-19 remains an urgent task. Mass testing for antibodies is necessary to assess the dynamics of the formation of population immunity to a new coronavirus infection [1,2]. And this, in turn, will make it possible to understand in what period the restrictions imposed in connection with the pandemic can be relaxed. As the initial test for antibodies, it is recommended that blood be tested simultaneously for antibodies of classes M and G. Immunoglobulins of class M (IgM) are early antibodies that the immune system begins to produce in response to SARS-CoV-2 infection. Their level usually becomes available for detection no earlier than 1-2 weeks from contact with the pathogen (no earlier than 5 days from the onset of symptoms in a symptomatic course), and the total period of probable detection of class M antibodies is often less than 2-3 months. During this time IgM antibodies are gradually replaced by IgG. Detection of IgM, therefore, may indicate recent infection with SARS-CoV-2. However, the result of this test alone cannot serve as a basis for diagnostic conclusions. The level of antibodies and the dynamics of the antibody response can vary individually [3]. Class G immunoglobulins to SARS-CoV-2 begin to be detected in the blood about 3-4 weeks after contact with the virus (or 2-3 weeks after the onset of symptoms), sometimes they appear almost simultaneously with IgM, the level remains available for determination more 10 weeks. By the presence and level of IgG antibodies in the blood, one can judge the fact of infection in the past and, possibly, determine the presence of a specific immune response - the ability of the body to recognize the virus when it meets again [4,5]. Currently, there are universal test systems that give a result in the form of an index of the positivity coefficient, which also needs to be deciphered by the diagnosis. The development of an automated diagnosis system for COVID-19 will help solve the problem with early diagnosis of the disease [6,7].

2. Equipment and devices used in studies
The theory of virology, finite automata and relay-contact circuits was used to build a model of the device. For the software and hardware part, it is proposed to use the industrial controller Omron-CP1L.

3. The results of the study and their discussion

3.1. Building a graph of the probability of human health states
The general model of infection and the course of the disease can be described by the graph of states and transitions shown in Figure 1. During the active stage of the disease, antibodies M are produced, during recovery, antibodies G appear and antibodies M are also observed. The end of the disease is characterized by the presence of antibodies G, which characterize the presence of immunity. Currently, the duration of the presence of G antibodies and the possibility of recurrent disease are being clarified.

3.2. Development of a diagnosis recognition module
To develop an operational monitoring system based on the graph of states and transitions (figure 1), we will compile a truth table for the operation of the express analysis device for the presence of antibodies M and G. The result of the analysis can take seven states, including:

- negative reaction (R1);
- a positive reaction (active phase of the disease) (R2);
- passive phase of the disease (R3);
- invalid analysis result (R4);
- questionable analysis result (R5);
- positive reaction to antibodies G, a previous disease (R6);
- reference (borderline) interval of the positivity coefficient M (R7).
Active stage of the disease

Recovery

Development of immunity

Figure 1. Graph of health states and transitions depending on the presence of antibodies M, G.

To build a device diagram, it is necessary to specify blocks of input and output signals. The block of input signals (table 1) will contain three signals In (X1, X2, X3).

Table 1. Block of input signals.

| Signal | Description                  | Address |
|--------|------------------------------|---------|
| X1     | Presence of antibodies M    | 2.00    |
| X2     | Presence of antibodies G    | 2.01    |
| X3     | Analysis control            | 2.02    |

The block of output and intermediate signals Out (R1, R2, R3, R4, R5, R6, R7, R71, R72) is shown in table 2.

Table 2. The block of output and intermediate signals.

| Signal | Description                                           | Address |
|--------|-------------------------------------------------------|---------|
| R1     | Negative reaction                                     | O: 101.00 |
| R7     | Reference interval M (positivity coefficient is in the range 0.8-1.1) | O: 101.06 |
| R2     | Positive reaction. Active phase of the disease         | O: 101.01 |
| R3     | Positive reaction. Passive phase of the disease        | O: 101.02 |
| R4     | Invalid analysis result                               | O: 101.08 |
| R5     | Questionable analysis result                           | O: 101.04 |
| R6     | Antibody G positive                                   | O: 101.09 |
| R71    | Intermediate signals (positivity coefficient M is in the range 0-1.1) | 3.00 |
| R72    | Operational value M                                   | 3.01    |
| Data memory area | Minimum border of reference interval M | D300 |
|        | Maximum border of reference interval M                | D301    |

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3.3. Analysis of device control logic

The M antibody sensor, depending on R71 and R72, can take borderline negative or borderline positive results. To compile the truth table, we will assume that "L" will correspond to the positivity coefficient (Kp) M <1.1 with further analysis of the borderline, positive and negative results (R71, R72), and "T" - the state Kp ≥ 1.1 - a positive result (R6).

The developed truth table showing the mapping of a set of input signals In (X1, X2, X3) to a set of output signals Out (R1, R2, R3, R4, R5, R7, R71, R72) is shown in Table 3.

| Monitoring sensors | Diagnosios |
|--------------------|------------|
| X1 | X2 | X3 | R71 | R2 | R3 | R4 | R5 | R72 |
| L  | L  | L  | L   | L  | T  | L  | L  | L  |
| L  | L  | T  | T   | L  | L  | L  | L  | L  |
| L  | T  | L  | L   | L  | T  | L  | T  | T  |
| T  | L  | L  | T   | L  | L  | T  | L  | T  |
| T  | L  | T  | L   | L  | T  | L  | T  | L  |
| T  | T  | T  | L   | L  | T  | L  | T  | L  |
| T  | T  | T  | L   | L  | T  | L  | T  | L  |

In accordance with table 3, the logical expressions were minimized and the logical equations of the analyzer unit operation were obtained (table 4).

| № | Analysis results                                      | Logical equations               |
|---|-------------------------------------------------------|---------------------------------|
| 1 | Reference interval, negative reaction                 | $R71 = \overline{X}1 \cdot \overline{X}2 \cdot X3$ |
| 2 | Positive reaction. Active phase of the disease         | $R2 = X1 \cdot \overline{X}2$    |
| 3 | Positive reaction. Passive phase of the disease        | $R3 = X1 \cdot X2$               |
| 4 | Invalid analysis result                               | $R4 = \overline{X}1 \cdot \overline{X}2 \cdot \overline{X}3$ |
| 5 | Questionable analysis result                           | $R5 = \overline{X}3(X1 \vee X2)$ |
| 6 | Reference interval, previous disease                  | $R72 = \overline{X}1 \cdot X2$   |

The analysis of signals R71 and R72 depending on Kp M will be described by graph-scheme, shown on figure 2.

![Figure 2. Graph-diagram of signals of reference intervals R71 and R72 depending on Kp M.](image)

3.4. Building ladder diagrams and device operation simulation

Omron-CP1L controller was chosen to build a model of the express analyzer. The development of ladder diagrams of the device based on logical equations (table 4) was carried out using CX-
Programmer module. The description of the operation of the simulation of the express analysis diagnostic scheme is given in table 5.

**Table 5.** Description of operation of relay-contact express analysis scheme.

| №   | Operator’s monitor | Ladder diagrams (LD) |
|-----|--------------------|----------------------|
| 1   | Signal “C” is not activated, invalid analysis result |
| 2   | Positive reaction. Active phase of the disease |
| 3   | Negative result |

4. Conclusion
A project was developed for an express analyzer device for analyzing human venous blood samples for the presence of immunoglobulin M and G antibodies. The use of the industrial controller Omron-CP1L, given its wide use in medicine, is economically feasible to design a series of devices for the
determination of COVID-19 antibodies. A module for the express analyzer of the device was developed. The analysis and synthesis of logical equations based on the minimization of the disjunctive normal form of logical expressions is carried out. An operator-diagnostician interface was developed. The simulation of the operation of the device circuit showed satisfactory results in determining the preliminary diagnosis of the disease.

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