Two Antigenically Indistinguishable Viruses in a Population

Radoslaw Nielek, Aleksander Wawer, Romuald Kotowski

An expanded model describing viral evolution within organism was proposed as an extension of the SEIRS model with illness symptoms - SEI[Is]RS. It has been implemented in a self-organizing, multi-agent system based on social networks and social time model. This article presents the results of simulation of simultaneous spreading within the population of two viral strains which provide total cross immunity to each other. The effect of displacing one viral strain by another, supported by empirical observations, is also present in obtained simulation results. It might have important consequences for genetic and antigenic diversity of viruses in populations.

Epidemic, SEIRS, virus spreading, social network,

I. Introduction

The work regarding modeling of disease spread in populations had been carried out as early as in the 18th century by Daniel Bernoulli [1], even before Louis Pasteur suggested that diseases might be caused by microorganisms. Together with the development of information technology and numerical methods of solving equations there appeared possibilities to build and analyse more and more complex epidemiological models, for example with a probabilistic mechanism of transition between disease stages [2].

This article presents the results of simulated presence of two viruses in the population which provide mutual 100% cross immunity. Such scenarios occur in case of fast mutating viruses, such as the influenza virus. The research on the second immunological response [3] indicates that this may also be the case for a wider range of viral subtypes, significantly different genetically, especially in a short period after recovery. Special attention was paid on attempting to explain empirically observed displacement of one viral strain by another. The possibility resulting from this phenomenon to use an appropriately modified virus as a vaccine was also analysed. The studies were conducted with a multiagent system, designed for this simulation, and SEI[Is]RS as the model of viral evolution in the body, described in the subsequent parts of this article.

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II. SEI[Is]RS – A NEW MODEL OF VIRUS EVOLUTION

SIRS (Susceptible – Infected – Resistant - Susceptible) and SEIRS (Susceptible – Evolution – Infected – Resistant - Susceptible), are the two most popular models of virus evolution in the organism, used to simulate incidence of non-mortal diseases. The modification proposed in this article is based on the addition of another stage, namely, "illness symptoms". Individuals limit their social activities during this stage. One can express this as a decrease in the number of their daily contacts with other individuals. It is explained by at least two interacting effects: a lower amount of energy due to disease symptoms and social responsibility – "I am limiting myself from contacting others because I don't want to infect them". The effects related to changes in the behaviour of individuals due to a disease or only information about a disease are considered by some authors to be incurring the highest economic costs for the society [4], sometimes even higher than the outbreak of pandemic itself.

The length of virus evolution stages are variable and depend on many factors in reality. According to the research done in this field, disease stages can change many times as a result of taken medications, genetic conditions, diet or a wide range of external and internal factors. The model of bi-directional, probabilistic transitions between disease stages was presented for AIDS in [2].

Fig. 1 presents the sequence of virus evolution stages in the organism which was used by the authors of the article to simulate epidemic. The values marked on the OX axis with Greek letters are set as simulation parameters. All individuals in stages "evolution", "infectious" or "illness symptoms" are infected. Transitions between stages are possible only in one direction. The model does not take into account differences between individuals regarding their resistance to illnesses or their recovery rates.

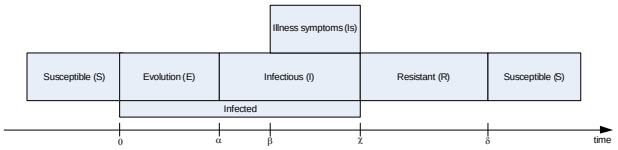

Fig. 1. *Virus evolution in an individual with the time.*

As the model takes into account non-mortal diseases caused by fast mutating viruses, the resistance acquired by an individual after experiencing a disease is only temporary. It is related to the immunological memory of individuals, which weakens with time since the last virus infection, for most but

not all diseases. Appearance of new mutations of a given virus is the second factor limiting the time of individual immunity.

Advantages of the extension of a virus evolution model in the organism with the *illness symptoms effect* are noticeable especially in multiagent systems, where the limitation of individual activities can be directly reflected in the changes of a structure of each agent's daily contacts.

III. SIMULATION ENVIRONMENT

In the real world, every individual maintains contacts only with a low fraction of the population. Obviously, the number of contacts depends on a person and individual traits of character, mood, and other factors, although the influence is weaker than it might seem. Research by Lopes [5] shows that social competence (emotional intelligence) and general well-being (satisfaction or depression) have a very limited influence on the number of daily contacts. However, these factors influence the quality of these contacts what may be significant during the attempts to simulate virus spreading related to a specific type of behaviour – AIDS.

Each individual may be in a different stage of the disease or resistance to the disease; moreover, every day they meet with a limited group of the acquaintances. The necessity to take into account specific features of different agents, as well as the intention to observe results on the population level, multiagent systems were chosen as the base of a simulation system.

Networks are a recognized way of modelling contacts between population members. However, there is no unanimity regarding their type. Simulation of epidemiological phenomena is performed in networks of the crate structure or random networks [6][7], as well as in scale-free networks [8][9]. Interesting results regarding virus spreading in small-world networks were achieved in [10]. They indicate that realistic simulation results can be obtained for quasi random graphs and not for crate-based. Also large-scale attempts to compare results depending on a network type have been undertaken [11].

The results for crate-structure networks or random networks indicate existence of an infectiousness threshold, exceeding it results in the outbreak of a pandemic. The values below this threshold result in quick disappearance of the virus from the population. Such a threshold does not exist in scale-free networks, which puts in doubt the plausibility of achieved results. Some authors postulate including clusters into the structure of these networks [12], which resolves this problem to some extent. However, a theoretical explanation of cluster presence in social networks is not known, at least not in daily contacts networks. Moreover, networks with this structure cannot be regarded as fully corresponding to the structure of daily contacts.

The proposed solution of these problems, a system capable of simulating daily activities of agents (individuals in the population), has been described in this work. Similar attempts, to a limited extent however, as they distinguish only two classes of activities, namely home and work activities, were presented for example in [13] and [14]. The network structure in the proposed system is not preconstituted or assumed artificially (one of the assumptions of the model!), but is formed as the result of interactions between agents.

The model used in simulation consists of agents (subjects undertaking activities) linked by edges (acquaintanship) which represent the possibility of scheduling activities together. Edges have one attribute – weight – a number from the interval (0,1] describing their strength. Specifically, the model is a non-directed graph. Additional attributes of the model are the list of communication topics S_{pop} and the set of time frames T_{pop}, when scheduling common activities can occur. The example interpretation of elements in sets T_{pop} and S_{pop} could be made in a following way:

$$S_{pop} = \{love, football, \ldots\}$$
$$T_{pop} = \{Monday, Thursday, \ldots\}$$

The vector $\boldsymbol{s}$, describing the unique willingness to spend time on every topic, is attributed to each of the agents; moreover, each agent has a personal diary $\boldsymbol{t}$, which is filled by arranging appointments with neighbours from the social network. The edges linking individuals with whom attempts to meet are successful are enhanced, whereas others are weakened. If the edge strength falls below the threshold value (it is unused for a certain period of time), such edge is removed.

The last mechanism shaping the social network are the heuristics allowing creation of new acquaintances (contacts). There are two of them implemented in the proposed system: "my friends' friends are more likely to become my friends" (transitive relation) and "accidental meetings" (random). The strength of these heuristics to influence the network shape is one of the parameters of the model– NE_{h1} and NE_{h2}.

Rounds are the units that organize time in the system. One round consists of predetermined, fixed number of time frames, the same for all individuals. Within a round, individuals try to fill in their diaries with meetings. After each round the individuals' diaries are cleared off and their individual willingness for discussion is refreshed. The length of individuals' diaries and the number of meeting attempts are the parameters of the model. The interpretation of the notion 'round' in the categories of typical time measures such as hours, days, weeks, depends on the values of these variables. These parameters in the simulations performed for this article were chosen so as one round would correspond to one day, approximately.

In the current system there are no environmental virus spores, therefore it can persist only as long as there are infected individuals within the population. Virus transmission is possible when two individuals, one infected and one susceptible, meet.

IV. Results

The epidemic outbreak should result in a decrease in the total number of daily contacts in the population. Two main reasons for this effect might be observed:

- some people are ill, therefore, they limit their activities (lack of energy)
- some people, under the influence of information about the epidemic, do not send their children to schools, kindergartens, go out more rarely etc.

In the experimental model only one, namely the first condition is implemented as it is closely related to the suggested expansion of the SEIRS model. The simulations performed indicate that the presence of a virus has an influence on the shape of the social network: its density decreases. The difference visible on the *Fig. 2* depends on viral parameters, namely, the stronger and longer-lasting disease symptoms are, the larger the difference is; as well as on the rate of edge fading.

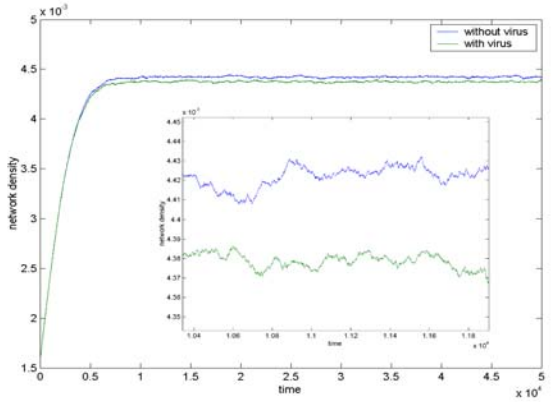

Fig. 2. *Network density in the system depends on the presence of a virus in the population. It is higher in the case without a virus. The difference depends on the parameters of a specific virus, including the strength of illness symptoms. Even when the system has stabilised there are still changes in the network for both these cases what may be observed in the magnification of a graph fragment. The correlation between signals at the level of 0.1879.*

As presented on the chart of the network density, even when the density has stabilized, there are still fluctuations in the system caused by new edges appearing and old ones disappearing.

The network structure obtained as a result of agent interactions resembles a random network. However, the histogram of the edge number reveals a normal distribution. The mean density of the achieved network depends on many parameters, including those related to a virus; whereas, the mean strength of edges depends directly on the amount of new edges NE_{h1}, NE_{h2}, but it does not depend on the network density – the correlation is at the level -0.0982. The mean edge strength also shows a little negative correlation with the mean number of free days -0.2986. The correlations are statistically significant.

The effects of presence of two viral strains providing a partial, mutual immunity to each other in the population were studied by many researchers [15]. However, the literature regarding viruses ensuring 100% cross immunity is much smaller. It is so due to large difficulties in identification of such viruses, as 100% cross immunity means that they are indistinguishable in terms of antibodies produced by an infected organism. This effect considerably limits the possibilities of studying such viruses in the real world. For that reason, computer simulation allowing to study such cases becomes even more significant in this case. Existence of vaccines indicates that there might exist viruses which are antigenically indistinguishable which, however, differ in terms of disease symptoms they cause.

The first simulations were carried out for two viruses identical in terms of start-up parameters. Both viruses were injected into the population at the same round and in the same amount. Individuals infected with viruses are chosen randomly, therefore it may happen that one of those strains will be in a cluster which is isolated from the rest of the network. For that reason, in order to receive plausible results, the simulations were repeated many times for the same set of parameters.

At 1000 individuals and 100 simulation repetitions only in one case both viruses survived 5000 rounds. In all other cases only one virus remained in the population, displacing the other. Fig. 3 illustrates this process. It is worth observing that according to the predictions both viruses had almost the same chance to be displaced – 0.49 for the first and 0.50 for the other virus.

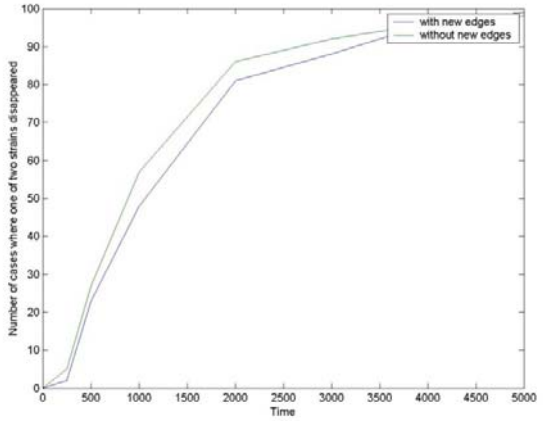

Fig. 3. *Dynamics of displacement of one viral strain by another.*

In a great number of cases this competition is settled in 2000 rounds, which can be seen in Fig. 3. Moreover, subsequent studies show that this moment is not significantly related with the size of the population. Even its doubling does not have a visible effect on the rate of displacing one strain by another. After taking a closer look at the single cases where both viruses coexist the reasons of such a behaviour still cannot be fully explained. The parameters, such as network density, number of meetings, distribution of topics or a

histogram of the number of edges have similar values in case of all simulations. A small number of such special cases makes it additionally difficult to perform any statistical analysis.

It seems that such an atypical behaviour of viruses is caused by a very specific structure of the social networks in these simulation runs, introduced by the very design of the multiagent system; however, it is very unlikely. This network probably consists of two poorly connected subgraphs. Subsequent experiments were conducted in order to study the effect of factors responsible for mechanisms of creating and modifying social networks present in the model on displacing one viral strain by another. Simulations were repeated with different shapes of edge enhancing and suppressing functions, which corresponds to the efficacy of individual's memory as well as to different strength of heuristics creating new edges – NE_{h1}, Ne_{h2}. The results show that these parameters have almost no impact on observed disappearance of one viral strain. The results presented in the Fig. 3 for the systems with- and without adding edges show that the differences are not of a system nature, but they are caused by stochastic processes within the model and differences in the network density.

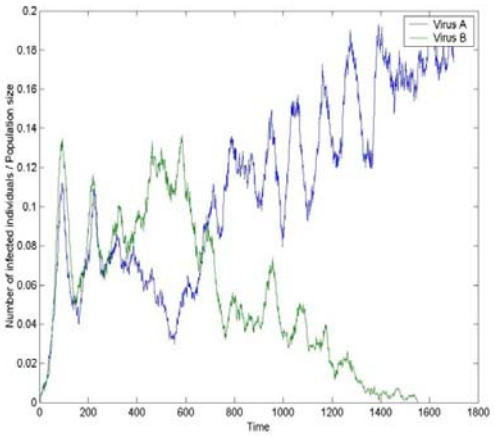

Fig. 4. *Mutual displacement of viral strains in the population.*

A typical course of epidemics with two viruses in the population shown in the Fig. 4 indicates that until one virus strain has been displaced by another, winning of this competition is settled neither at the beginning nor even in the first rounds. The fact that graphs cross each other several times proves that this process is much more complicated and even once a significant asymmetry in the number of infected individuals between strains has been achieved, it is still not a sufficient condition for winning of one strain. It is most likely that it is also due to some specific environmental conditions, a local shape of the social network and the combination of these factors result in an effect of displacing one virus by another.

The effect of displacing one virus by another is present also in a situation when viruses appear in the population at different time periods. The virus that appears as the first is more likely to win the competition. Out of 100 cases only in 3 of them the virus which appeared later displaced the previous one. The results reveal certain degree of sensitivity as to the moment when a new virus appears in the population. If it is injected at a time when there is a minimal incidence of disease cases of the virus already present in the population, the chances for survival of a new virus are two times higher. Nonetheless, this likelihood is still low and equals approx. 0.06.

V. Discussion

When Kamo and Sashaki [16] conducted research describing the SIR model expanded with effects of the virus spreading dynamics dependent on seasons, they concluded that for almost all values of the cross-immunity parameter, except for the extreme values, two viral strains coexist with each other in the population. Theirs studies show that even in the case of large differences in the values of the infectiousness parameter, the SIR model tends to promote coexistence of different strains. However, Ferguson and Bush [17][18] indicate that differentiation of influenza viruses, both genetic and antigenic, observed nowadays is surprisingly small. Especially when one takes into account the lack of correction mechanism in the form of the second RNA strand in influenza viruses. Their studies indicate that cross-immunity alone cannot be considered a mechanism which ensures an adequately high level of competition between influenza virus strains to explain slight differentiation which is observed. The suggested explanation is the second immunological response, which is not only heterosubtypic but also heterotypic.

Levin et al. [19] quoting some research argue that for fast mutating viruses based on RNA, there are usually clusters of strains differing genetically and antigenically to a limited extent. Those authors tried to group available sequences of influenza virus strains based on the measure of Hamming likelihood. The results superimposed on the dates of strains domination belonging to specific clusters in the population show that the dominating cluster changes every 2 – 5 years.

The results reported by the authors of this article seem to follow all previously mentioned studies. Anomalies indicated by Kamo and Sashaki in the results of equations of the SIR model for 100% cross-immunity resulting in displacing one strain by another also occur for the extended SEI[Is]RS model implemented in the multiagent simulation and time-based arrangement of agents' meetings. In addition, repeated simulation runs proved that the effect of a total displacement is present. For the stochastic system described in this article, the reverse situation (no displacement) occurred with the likelihood lower than the value determined from simulation, namely 0.05. This effect is also present when one of the strains was already present in the population while the other one appeared. The strain that bears the palm in significant majority of cases displaces the new; however, in those cases where it is not possible, it is being displaced as shown in Fig. 5.

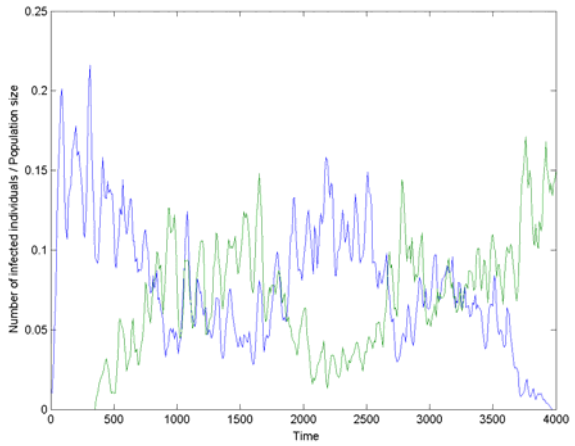

Fig. 5. *Two competing with each other viral strains with the same infectiousness and length of separate stages, ensuring mutual cross-immunity of 100%.*

Publications on the second immunological response in humans, for example [3], argue that almost 100% cross-immunity is not a fiction and it exists also among viruses which are not identical neither genetically nor antigenically, at least during short periods after a disease. The studies by Thieme [20] conclude that even a relatively short period of 100% protection against re-infection provided by the second immunological response may significantly affect the presence of seasonal oscillations. In this context the achieved results may, to some extent, explain the problem of little differentiation between influenza viruses raised by Ferguson and Bush [17]. The limitation of the re-infection rate suggested by them may be achieved not only by a suitably higher level of cross-immunity but also by "illness symptoms" (Is) and expanding the SIR model to SI[Is]RS or SEI[Is]RS. As far as humans are concerned, *Is* may be understood not only as a change in the behaviour due to direct disease symptoms but also as a change of attitudes and behaviours regarding one's own health and activity which is extended in time and lasts after disease symptoms have ceased.

Moreover, a very strong domination of one of the two identical strains in terms of infectiousness is presented in analytical solutions [16] as well as in simulations, as this article shows difficulties regarding containing higher differentiation of influenza viruses. Basing on the simulations conducted it may be estimated that the probability of a situation, when a new strain with the same parameters as the previous one increases differentiation of influenza viruses and coexists with the ones existing so far in the population is below 0,001. This calculation is based on the empirically obtained probability of survival of a virus injected into the population already dominated by the existing strain and on the possibility that two viruses with similar parameters will coexist. These calculations do not take into account the probability of mutations which create such a virus. The hypothesis about high similarity or even identity of parameters, characterising a mutated influenza virus, such as infectiousness, seem to make sense as new influenza strains appearing every year do not differ significantly in regard to parameters of their spreading.

The research of Levin et al. indicating mutual displacement of clusters relatively similar to one another of influenza viruses in the period of 2 – 5 years seems to verify the accuracy of the created model. Displacement of one virus, which in this case may be treated as a cluster of mutations similar to each other, by another one usually occurs between 500 and 2000 rounds what can be seen in Fig. 3. Referring to tbe discussions performed before introducing time in this system, this interval may be a rough counterpart of the period suggested by Levin et al.

VI. Summary

Supplementation the virus evolution model with illness symptoms (Is) allows to explain better empirically observed and lower than expected number of individuals reinfected with another subtype of a given virus. If we agree with the thesis that changes in behaviours due to disease symptoms may occur after the regression of symptoms themselves, this effect may be accepted as fundamental for the likelihood of the next pandemic outbreak.

The achieved results also indicate inapplicability of a mathematical description of the world and social interactions. Numerical solutions of equations by no means bring us closer to results achieved thanks to simulation in the multiagent environment. These differences are not only quantitative but also qualitative. In this context averaging results for many repetitions of simulations with the same parameters for explanatory purposes seems to be methodologically incorrect, as it eliminates the randomness factor, which affects strongly one community one community and one virus.

The achieved results stimulate to raise subsequent research problems, such as for example creating a virus-vaccine which can spread itself, displacing more dangerous microorganisms. What are the optimal properties of such a virus and what are the most effective ways to inject it into the society? This idea in connection with the model of displacement of one virus by another within the organism suggested for example in [21] may allow for constructing effective strategies to deal with epidemics.

Yet another idea is to use the degree of intimacy – edge strength – and type of activity – topics of meetings – to simulate diseases spreading of which is connected with a specific type of activity, for example sexually transmitted diseases. An appropriate choice of the proportion of intimate topics to all topics in the population would solve the problem raised in [22] on inapplicability of the *a priori* statement regarding monogamy of the community for which this simulation is being performed.

All these studies and results contribute into understanding crucial factors influencing virus spreading and potential

scenarios of pandemic development. However, it seems that until biologists are able to describe precisely what the course of the virus infection is in the body and what factors influence its course and programmers are able to simulate such complex systems, we will not be able to answer the question whether John Doe will catch flu this season.

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