Advanced selection of ideal building blocks for ‘‘smart’’ biocompatible surfaces: prediction and study of polymer properties and streaming video recognition method for observation of the cellular behavior and economic effect

Yurij Stetsyshyn [0000-0002-6498-2619], Uriy Kryvenchuk[0000-0002-2504-5833], Yuliia Chyrkova [0000-0001-7315-9520], Tetiana Helzhynska[0000-0003-3280-5199], Pylyp Skoropad [0000-0003-3559-6580], Liubomyr Pohreliuk[0000-0003-1482-5532], Yurij Panchenko [0000-0003-1760-177X]

Lviv Polytechnic National University, Lviv 79013, Ukraine
yrstecushun@ukr.net, yurii.p.kryvenchuk@lpnu.ua, yuliia.l.chyrkova@lpnu.uatanyazvarich@ukr.net, skorfil@yahoo.com,liubomyr@inoxoft.com, yupanchenko1@gmail.com

Abstract. In this work we developed some aspects for advanced selection of ideal building blocks for ‘‘smart’’ biocompatible surfaces using prediction of polymer properties from additive group contributions. Especial interest was included in prediction of wettability and surface energies of “smart” polymer brush coatings which may strong impact on many biological processes rely on feedback-controlled interactions with biomolecules and cells. Idea for identification of another crucial aspect for application of the polymers as biocompatible materials, behavior of the cells was developed using streaming video recognition method.

Keywords: Streaming video recognition method, cellular behavior, prediction of polymer properties.

1 Introduction

Nowadays, information technologies and artificial intelligence offer lots of opportunities for chemical, physical, biological and material sciences. Polymers form an important, amazing and challenging class of the materials. They are widespread with applications ranging from daily products, e.g., plastic packaging and containers, to know-how, e.g., high-energy density capacitors, polymer light-emitting diodes, controlled release dosage forms and “smart” biomaterials. Their chemistry and morphology are extremely vast and complex, leading to fundamental barriers in polymer studies. Recent successes in rationally designing polymer as biomaterials via experiment-computation synergies indicate that there may be opportunities for theoretical prediction, machine learning, informatics approaches and advanced technologies in this new research and development area.

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One of most important trends in application of the polymer as biomaterials are surface modification with polymer brushes which allow to add to surfaces a valuable and desired properties. In the most general sense, polymer brushes are defined as thin polymer films in which the individual polymer chains are tethered by one chain end to a solid interface. Depending on the density at which polymer chains are anchored to the surface and their molecular weight, surface-anchored polymer chains can adopt various conformations, from the so-called "mushroom" or "pancake" regime at low grafting densities to the high density "brush" regime.

One of the most important characteristic of the grafted polymer brushes are surface wettability. Surface wettability is an important parameter and is the first that was controlled in almost all surface modification strategies. Wettability mainly depends on surface chemical functionality, although surface roughness also plays an important role. This phenomenon is closely related to another surface properties like reactivity, absorption, and even mechanical properties. In general, are numerous ways to modify surface wettability using polymer brushes, including grafting different types of polymer brushes, copolymer brushes, binary polymer brushes and using stimuli-responsive polymer brushes that able to change wettability upon an external trigger. In our opinion, modifications with different polymer brushes that are sensitive to surrounding area are the simplest way to change surface wettability. Prediction of the polymer properties allows to solve important questions about availability their application as biocompatible materials. As was mentioned before, one of most important properties are wettability that can be calculated theoretically but all parameters such as low critical solution temperature and other may be considered here.

To solve the problems described above we should use advanced theoretical predictions and machine learning technologies. We propose to use prediction of polymer properties from additive group contributions but the same time all possible polymer parameters should be considered to eliminate the possible errors. Another side our study is detailed analysis of biocompatibility (cellular behavior) that can be realized using streaming video recognition method.

2 State of arts

In the macromolecular area the amount of literature sources are extremely large but really often are problem that neither directly measured properties before or reliable methods to calculate them can not find. To predict properties of the polymers the simple and very successful method based on the concept of additive group contributions was firstly proposed by van Krevelen [1]. In general, thousands of chemical substances may be virtually decomposed to the number of structural and functional groups. The assumption that a physical property of a compound, e.g. a polymer, is in some way determined by a sum of contributions made by the structural and functional groups in the molecule or in the repeating unit of the polymer, forms the basis of a method for estimating and correlating the properties of a very large number of compounds or polymers, in terms of a much smaller number of parameters which characterize the contributions of individual groups. These group contributions are called as

increments. The basic assumption of the group-contribution method is additivity. This method was valid only when the influence of any one group in a structural unit of a polymer was not affected by the nature of the other groups that are essential limitation for this technique.

In this work we developed some aspects for advanced selection of ideal building blocks for ‘‘smart’’ biocompatible surfaces using prediction of polymer properties from additive group contributions. Especial interest was included in prediction of wettability and surface energies of “smart” polymer brush coatings which may strong impact on many biological processes rely on feedback-controlled interactions with biomolecules and cells.

Approach based on works developed by Girifalco and Good was used here [1]. Wetting contact angles were calculated using equations:

$$\cos\theta = 2\Phi\left(\frac{\lambda_s}{\lambda_l}\right)^{1/2} - 1 \tag{1}$$

$$\Phi \cong \frac{4(V_s \cdot V_l)^{1/3}}{(V_s^{1/3} + V_l^{1/3})^2} \tag{2}$$

where, Φ - ratio of liquid and solid molar volumes in Eqs.1 and 2

λ_s - surface tension of solid, mN/m;

λ_l - surface tension of liquid, mN/m (values from Tables);

V_s, V_l - molar volume of polymer and liquid, respectively (values from Tables).

Polymer surface energy was calculated using:

$$\lambda_s = \left(P_s / V_s\right)^4 \tag{3}$$

where, P_s – molar parachor (molar parachor is a useful means of estimating surface tensions); V_s - molar volume of polymer.

The parachor was introduced by Sugden, who first gave a list of atomic constants. Later the atomic and group contributions were slightly modified and improved by Mumford and Phillips and by Quayle (see Table 1) [1].

Calculation of the wetting contact angle and surface energy (surface tention) are presented by van Krevelen for solid poly(methyl methacrylate) (see fig. 1).

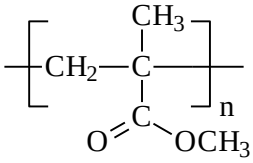

Fig. 1. Unit of poly (methyl methacrylate)

Table 1. Atomic and structural contributions to the parachor

Units	Values assigned by		
	Sugden	Mumford and Phillips	Quayle
–CH_2–	39.0	40.0	40.0
>C<	4.8	9.2	9.0
–H	17.1	15.4	15.5
–O–	20.0	20.0	19.8
–O_2 (in esters)	60.0	60.0	54.8
>N–	12.5	17.5	17.5
–S–	48.2	50.0	49.1
–F	25.7	25.5	26.1
–Cl	54.3	55.0	55.2
–Br	68.0	69.0	68.0
–I	91.0	90.0	90.3
Double bond	23.2	19.0	16.3–19.1
Triple bond	46.4	38.0	40.6
Three-membered ring	16.7	12.5	12.5
Four-membered ring	11.6	6.0	6.0
Five-membered ring	8.5	3.0	3.0
Six-membered ring	6.1	0.8	0.8

Table 2. Contributions of the functional groups of poly(methyl methacrylate) to the parachor

Units	Parachor [$(mN/m)^{1/4}\times(cm^3/mol)$]	Calculation
1 –CH_2–	39.0	
1 >C<	4.8	
2–CH_3	112.2	$2\times(CH_2+H)=2\times(39.0+17.1)$
1 –COO–	64.8	$1\times(C+O_2$(in ester))=(4.8+60)
	220.8	

Molar volume of polymer was taken from Tables in [1] and equal to 86.5 cm^3/mol. Contributions of the functional groups of poly(methyl methacrylate) to the parachor were calculated in Table 2.

Polymer surface energy was calculated with Eqs. 3 as $(220.8/86.5)^4$ and equal to 42.5 mN/m.

According to Eqs. (2), where V_l (molar volume of water) is equal to 18 (value from Table in [1]) calculated Φ=1.

In turn, using Eqs. (3), where λ_l for water is 72.8 (surface tension of liquid) the contact angle with water (cos θ) was determined as: $2\times1\times(42.5/72.8)^{1/2}$-1=0.42 so that $\theta\approx65°$.

An experimental value of wetting contact angle for poly(methyl methacrylate) ($\theta\approx$ 67°) has been published by Ma [2], which is in good correspondence with theoretically calculated.

To continue mentioned above analysis, poly(*N*-isopropylamide) – (p*N*IPAM), poly(di(ethylene glycol)methyl ether methacrylate) – (pOEGMA188), poly(*N*-methacryloylleucine) - (pNML) were selected (see. Fig.2). All presented here polymers are thermoresponsive and able to temperature-induced transitions which are expressed as reorientation of the polymer macromolecules (conformational changes) resulting in essential changes of wetting *etc*. Temperature-responsive changes for these polymers are based on low critical solution temperature (LCST).

First presented here polymer - PNIPAM are perhaps the most heavily studied thermoresponsive polymers. Although this group consists of few tens of the thermoresponsive polymers, only poly(N-isopropylacrylamide) and its copolymers have practical applications. In modern literature, there are numerous references devoted to this polymer, and special attention is paid to poly(N-isopropylacrylamide) (pNIPAM) grafted brushes. LCSTs of the pNIPAM and its copolymers are nearly 32 °C, which is close to the physiological temperatures of the human body. pNIPAM has been utilized in various biomedical applications such as biosensors, thermally modulated drug and gene delivery systems, pNIPAM conjugated proteins for thermally modulated enzyme function *etc* [3-9].

Second polymer, poly(di(ethylene glycol)methyl ether methacrylate) – (pOEGMA188) are biocompatible, uncharged, water-soluble, nontoxic, nonimmunogenic and therefore the most commonly applied synthetic polymers in the biomedical field [10-11].

Last presented here polymer is pNML which is based on natural amino acid. Application of pNML as the “smart” polymer offers at least two advantages: firstly, the leucine fragments of PNML, unlike other synthetic polymers, can provide peptide-mimetic properties for a polymer [12]. Secondly, the phase transition temperature of PNML can be tuned by modification of the free carboxyl groups. Moreover, free carboxyl groups can be further used for the attachment of biomolecules.

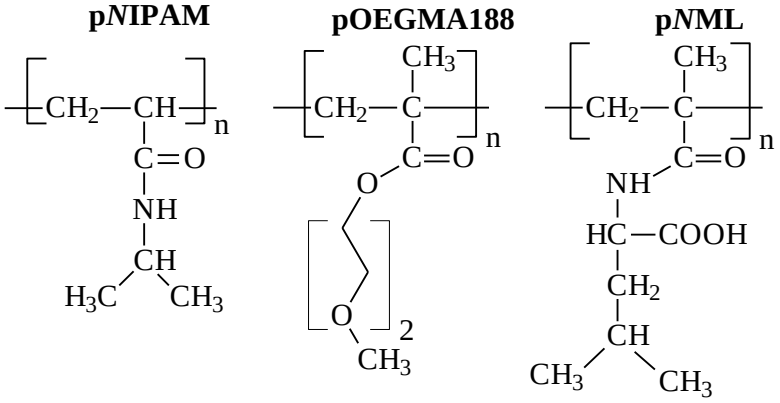

Fig. 2. Chemical structures of some polymers for biomedical applications.

In Table 3 are presented values of molar volumes and parachors described above polymers and calculated wetting contact angles in according to to Eqs. (1) and (2).

Table 3. Molecular volumes, parachors and calculated wetting contact angles for presented above polymers

Polymer	Molar volumes [cm^3/mol]	Parachor [$(mN/m)^{1/4}\times(cm^3/mol)$]	Calculated θ [deg]
pNIPAM	107.6	290.2	≈56
pOEGMA	160	411	≈69
pNLM	173.3	424.9	≈76

Calculated wetting contact angles were compared with experimental wetting contact angles obtained in our previous works [12-14]. Figs. 3-5 show the temperature dependences of the wetting contact angles for the pNIPAM, pOEGMA and pNLM grafted brush coatings, respectively. As we can see, values of the wetting contact angles for pNIPAM and pNLM at top of the curve are in good accordance with theoretically calculated (see Table 3).

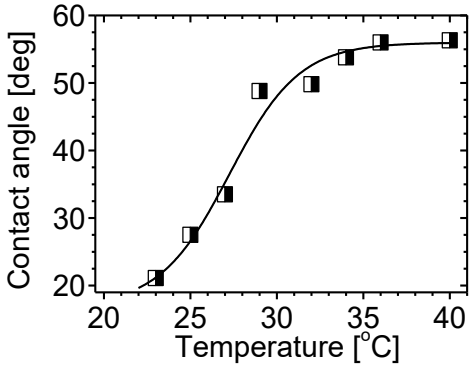

Fig. 3. Temperature dependences of the wetting contact angles for the pNIPAM grafted brush coatings. Solid lines are guide for eyes.

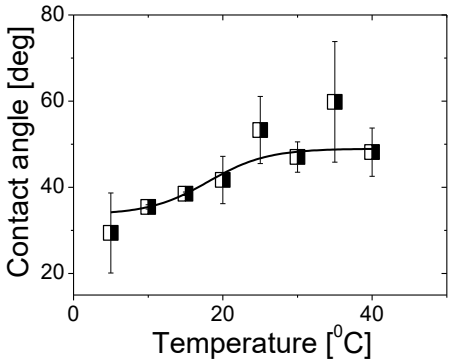

Fig. 4. Temperature dependences of the wetting contact angles for the pOEGMA grafted brush coatings. Solid lines are guide for eyes.

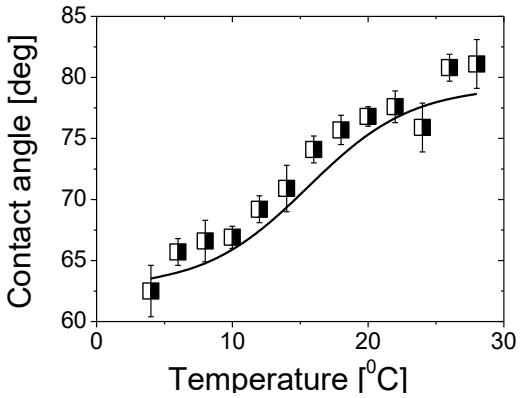

Fig. 5. Temperature dependences of the wetting contact angles for the pNML grafted brush coatings. Solid lines are guide for eyes.

In contrary, for pOEGMA calculated value is essentially another than experimental. For all cases, temperature-induced changes with sharp transition at are visible. Presented above model are probably simple enough to pay attention to all parameters such as interaction with water and temperature-depended interaction with water, in these cases named as the low critical solution temperature (LCST). Presented above curves demonstrate the changes in wetability during increasing of the temperature. Additional parameters such as LCST may be included in model. LCST is temperature when the polymer molecules attract one another but not solvent [15-29].

For polymers that exhibit an LCST behavior in aqueous solution, the responsive polymer is soluble due to extensive hydrogen bonding interactions with the surrounding water molecules at temperature and restricted intra- and intermolecular hydrogen bonding between polymer molecules before LCST. Upon heating, hydrogen bonding with water is disrupted, and intra- and intermolecular hydrogen bonding/hydrophobic interactions dominate, which results in a transition in solubility. The transition temperature of a polymer in solution is one of the most important parameters to take into account when considering applications under a given set of conditions. For instance, many of the thermoresponsive polymers reported to have potential use in biomedical applications have transition temperatures between room temperature and body temperature. In grafted polymer brushes LCST induces transition from hydrated loose coils to hydrophobic collapsed chains. The LCST can be readily tuned by incorporating hydrophilic or hydrophobic character by copolymerization with hydrophobic or hydrophilic comonomers or end group transformations. By increasing the hydrophilic nature of the polymers, the overall hydrogen bonding ability of the macromolecules is increased, which leads to higher transition temperatures. Incorporating hydrophobic groups lowers the LCST. Furthermore, the addition of hydrophobic groups causes a disruption of the structure of water around the macromolecules. This enhances the interaction of hydrophobic species, further facilitating aggregation.

We would like omit here discussion about LCST as part theoretical model presented here but this moment may be developed in details to predict properties of grafted polymer brushes. Another important aspect to predict properties of biocompatible surfaces to have information on cellular behavior on different coatings [18, 30].

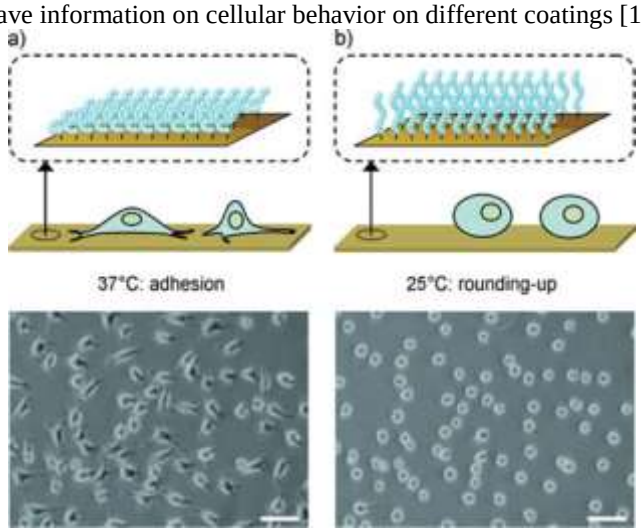

Fig. 6. Phase contrast microscopy images of L929 mouse fibroblasts on oligo(ethylene glycol)-based thermoswitchable substrates after 44 h of incubation at 37 °C (left) and 30 min after cooling the sample down to 25 °C (right). Scale bars correspond to 100 mm. Cartoons (top panel) show a schematic view of the polymer coatings at 37 and 25 °C [18].

Fig. 6 show phase contrast microscopy images of L929 mouse fibroblasts on oligo (ethylene glycol)-based thermoswitchable substrates after 44 h of incubation at 37 °C (left) and 30 min after cooling the sample down to 25 °C (right). Cartoons (top panel) show a schematic view of the polymer coatings at 37 and 25 °C. As we see, morphology of the cell is principally different at temperature transition from 37 °C to 25°C. It depends on sharp changes in physic-chemical properties of grafted brush coatings at relatively small changes in temperature. Analysis of the cellular behavior at dynamic observations is important aspect for understanding of the biocompatibility which may be realized using streaming video recognition method.

3 Streaming video recognition method

The analysis showed that for the recognition of groups of different objects or individual objects, the python is best suited as a programming language and a superstructure of pandas for pattern recognition. In the Python ecosystem, pandas are the most advanced and fastest growing library for processing and analyzing data. To work effectively with pandas, you need to master the most important data structures of the library: DataFrame and Series. Without understanding what they are, it is impossible to conduct a qualitative analysis in the future. You can often find ready-made solutions for face recognition in Python, but there is nothing on the network for cell recogni-

tion. Therefore, it was decided to adapt python libraries for such tasks. To do this, you need to understand the basic concepts.

3.1 Series

The Series structure / object is an object that looks like a one-dimensional array (a Python list, for example), but its distinguishing feature is the presence of associated labels, indexes, along each element of the list. This feature turns it into an associative array or dictionary in Python.

```
>>> import pandas as pd
>>> my_series = pd.Series ([5, 6, 7, 8, 9, 10])
>>> my_series
0  5
1 6
2 7
3 8
4 9
5 10
dtype: int64 >>>
```

In the string representation of the Series object, the index is on the left and the element is on the right. If the index is not explicitly specified, then pandas automatically creates a RangeIndex from 0 to N-1, where N is the total number of elements. It is also worth noting that Series has a type of stored elements, in our case it is int64, because integer values are transmitted. The Series object has attributes through which you can get a list of elements and indexes, these are values and index, respectively. A list with indexes in length must match the number of items in Series.

3.2 DataFrame

It is best to imagine a DataFrame as a regular table, and that's right, because a DataFrame is a tabular data structure. Any table always has rows and columns. The columns in the DataFrame are Series objects whose rows are their immediate elements. The easiest way to construct a DataFrame is to use the Python dictionary:

```
>>> df = pd.DataFrame({
... 'country': ['Poland', 'England', 'USA', 'Ukraine'],
... 'population': [17.04, 143.5, 9.5, 45.5],
... 'square': [2724902, 17125191, 207600, 603628]
... })
>>> df
    country      population   square
0   Poland23.04          2724902
1   England     143.50       17125191
2   USA          199.50       207600
3   Ukraine      23.50        603628
```

A DataFrame has 2 indexes: row and column. If the row index is not explicitly specified (for example, the column by which you want to build them), then pandas sets the RangeIndex integer index from 0 to N-1, where N is the number of rows in the table.

Access to rows by index is possible in several ways:

.loc - used to access by string label;

.iloc - used to access by numerical value (starting from 0).

Pandas supports all the most popular data storage formats: csv, excel, sql, clipboard, html. Most often you have to work with csv files. For example, to save our DataFrame with countries, just write:

```
>>> df.to_csv('filename.csv')
```

The to_csv functions still receive various arguments (for example, a separator between columns), which can be found in the official documentation for more details.

You can read data from a csv file and turn it into a DataFrame with the read_csv function.

```
>>> df = pd.read_csv('filename.csv', sep=',')
```

The sep argument indicates split columns. There are many more ways to form a DataFrame from various sources, but most often use CSV, Excel and SQL. For example, using the read_sql function, pandas can execute an SQL query and form the necessary DataFrame based on the response from the database.

3.3 OpenCV

OpenCV uses machine learning algorithms to search for cells in an image. Because the cell is so complex, there is no simple test that will tell you whether a cell has been found or not. Instead, there are thousands of little patterns and features to match. Algorithms break down cell detection tasks into thousands of smaller tasks, each of which is easy to solve. These tasks are also called classifiers. For something like a cell, you may have 6,000 or more classifiers, all of which must match the cell's detection (of course, within error). But therein lies the problem: the cell recognition algorithm starts at the top left of the image and moves down the small blocks of data, looking at each block, constantly asking, "Is this a cell?… Is this a cell?… Is this a cell?" Because the block has 6,000 or more tests, you may have to perform millions of calculations that stop your computer from stopping. To bypass this, OpenCV uses cascades. What is a cascade? The best answer can be found in the dictionary: “waterfall or series of waterfalls.” Like a series of waterfalls, the OpenCV cascade breaks down the problem of detecting cells into several stages. For each block it does a very rough and fast test. If it passes, a slightly more detailed test is done. The algorithm can have 30 to 50 of these stages or cascades and it will detect cells only then The advantage is that most images will return negative during the first few steps, which means that the algorithm does not spend time testing all 6000 functions. and on it. Instead of taking hours, cell recognition can now be performed in real time. Although the theory may seem complicated, in practice it is quite simple. The cascades themselves are just a bunch of XML files that contain OpenCV data that is used to detect

objects. You initialize your code with the desired cascade, and then it does the work for you.

What if you want to use a camera? OpenCV captures each frame from the camera, and then you can detect the cells by processing each frame. This task will require a powerful computer, because there are many frames and everyone needs to perform logical operations described above.

3.4 System architecture

However, not only the software part plays a key role in recognizing the behavior of cells. There is a need to develop a system for controlling cell growth, as well as to automate it. After conducting an analysis, it was decided to develop its own system, as there are almost no similar systems in the public domain in the world. Figure 7 shows the architecture of the cell growth control system.

On a substrate preliminary spend on all cases. They need to be believed at a temperature of 37 degrees Celsius, while the vibration temperature is not observed in the forge, and you need to increase the growth rate.

The microscope supports a high-speed picture that adjusts the program and information. The resulting usage is recorded as the current video for use with a high-resolution camera. The video stream is transmitted to the server, where it is further processed.

For the first time, the video is divided into frames for using OpenCV. Each frame is recognized in fast real time, in fact instantly receives information.

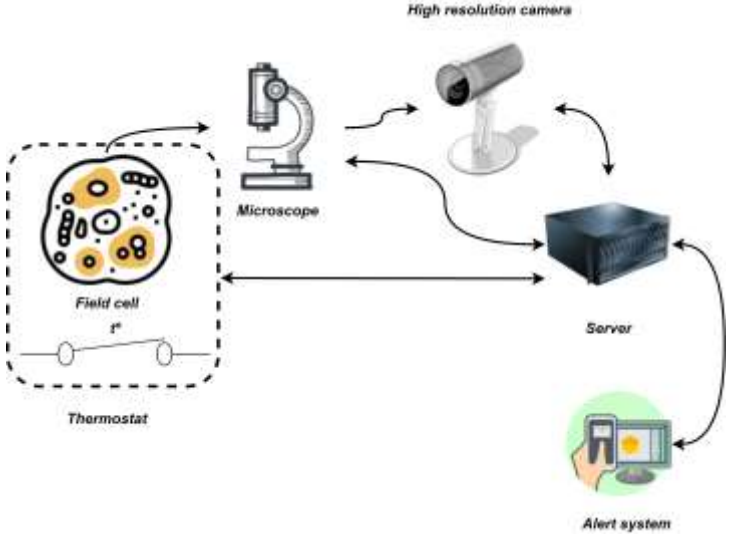

Fig. 7. Architecture of cell growth control system

The system monitors the growth of cells, and when the cell boundaries begin to approach each other, the system automatically corrects the temperature of the lining to 25 degrees Celsius. The cells begin to acquire an oval-shaped shape and detach from

the substrate. All manipulations with the thermostat, the camera, the recognized frames are logged on the server, and the system informs the laboratory assistant about the key moments.

4 Conclusions

Recent successes in rationally designing polymer as biomaterials via experiment-computation synergies indicate that there may be opportunities for theoretical prediction, machine learning, informatics approaches and advanced technologies in this new research and development area. In this work we developed some aspects for advanced selection of ideal building blocks for ‘‘smart’’ biocompatible surfaces using prediction of polymer properties from additive group contributions. Especial interest was included in prediction of wetability and surface energies of “smart” polymer brush coatings which may strong impact on many biological processes rely on feedback-controlled interactions with biomolecules and cells. Obtained results suggest that only complex approach including all possible parameters (not only parachor and molar volume but also LCST and interaction between polymer and water) of the polymer system may be successful applied to predict wetability and surface energy.

Another crucial aspect for application of the polymers as biocompatible materials are their biocompatibility based on cellular behavior. The analysis showed that today in the fields of biotechnology, chemistry there is no publicly available system that able successfully to observe the cellular growth and development. Manual control for such production processes is obsolete and increases the number of defects. The analysis showed that when automating the process of growing cells, the shortage will decrease by 29.3% compared to manual control (Figure 8). Also, in the future it is planned to modernize the system to ensure a minimum of human influence.

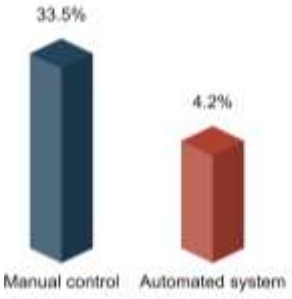

Fig. 8. The ratio of the number of defects in manual and automatic control.

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