DECOMPOSITION OF CELLULAR SYSTEM VIA CAUSAL RELATIONS

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Abstract

Time development of monolayer of the living cells represents the closest approximation to organ development and function. It inspired the computational approach of cellular automata and agent-based modeling. Yet, for description of the living cell this approach is seldom utilized. In this paper we address reasons why biochemical /molecular biology approach is so much more popular. We present the formal structure of stochastic systems theory for formal description of the cell culture experiment. We define phenomenological attributes of cell monolayer system as cell states assigned by the operator. As system variables we consider levels of metabolic fluxes in cell compartments and between them and states of intracellular signals. For example, cells composition and shape dynamics may be utilized as phenomenological system variables. Constituents are also all chemical individui detectable in the system. Components are sets of constituents which change independently, e.g. a set of chemical compounds bound together by a chemical reaction. In practical terms it means to determine all measurable – phenomenological – variables in sufficient time preceeding the change of state to assure that the state change is independent from any preceeding history. By counting the number of transitions and state lifetimes we obtain probability distribution functions for transitions between states. For the behavior of system variables we consider that of stable orbits in the state space which arise from movement in the confined intracellular space combined with chemical reactions. Recent theoretical studies indicate also that formation and maintenance of cell shapes may arise by similar mechanism. Bio-inspired computing has been a holy grail of computational theory since its eve. Recent developments in biological systems description open a question what is really meant by this term, how much the neural networks are related to neuron and cellular automata to cells. We address in this paper also the issue of reality of bio-inspired computing in production of adequate models and/or integration of living cell elements in the computational process.

Introduction

The cell state may be ultimately characterized by state of metabolic and signaling pathways, and by state of cellular structures. These two parameters complement each other. The pathways and metabolite transformations define and maintain the cellular structures. The current state of knowledge, does not allow to devise state of pathways from observation of structures and vice versa. Both phenomena are being observed experimentally in many routine experiments.

Any metabolite analysis contains the element of metabolite profiling and targeted analysis. It is always more than one class of compounds present in targeted analysis. There is never a complete metabolite profile. On to of that, the effective level of detection of, e.g. ions emitted from the electrospray source, depends on sample content, separation, ion source state, detector setup etc. The information content of the experiment needs to be examined locally and independently from any assumptions on the pre-assumptions on the sample.

The time-lapse microscopic imaging of cells is gaining increasing popularity with the introduction of fluorescent proteins such as GFP. Most of the experiments on living cells, in particular those which utilize cells derived from human patients, can not be contrasted by these highly advanced methods. Then the problem of observation and data analysis becomes similar to that of metabol(n)omics. The information content depends on sample pre-treatment as well as the quality of image capturing. In time cells changes in size, shape and observable morphologically contoured partitions, various in their shape, borders and light intensity.

The time-lapse microscopy experiment is the simple representation of biological cell dynamics. It is currently generally accepted that cell fate is best described by the chaotic attractor. The observable cell states represent individual basins of attraction. It is not quite clear in which relation the experimentally observable macroscopic parameters are to the state variables of the attractor space. In other words the experiment cuts the state space by its fraction, possibly lowering the space dimension, and of unknown shape - with respect to system coordinates.

Neither metabolite analysis nor the objective image dissection gives straight forward answer to diagnostic questions, similar to that expected from protein or m-RNA based biomarkers. This is caused by the fact that information content of these analyses is higher and provides deeper insight into the state of examined cells or cell cultures. Statistical analysis of time evolution of secondary metabolite contents or parallel changes in image contents represents time evolution of intercellular communication. With the increase of the throughput of both the metabolomic (Urban) and microscopic (Levitner) techniques, adequate automation of data analysis is becoming inevitable. The objective analysis of the information content of obtained data is an inevitable first step preceding any extensive pathway reconstructions, complex statistical evaluation etc.

One realistic approach towards objective analysis of the experiment is to determine evolution of information fluxes assessed by the experiment in time: Representation of information content of each timestep portrait. This representation is also in relation to dynamic biological system state in time of measurement. It is the map of information content in actual point in state space. Such detailed analysis is extremely computationally intensive, however, it might be of high value for rapid diagnostic in medicine, biotech-

nology, and any other discipline utilizing cell biology results.

Currently, there exist two complementary approaches to systems theory. One approach is to decompose the investigated system into subsystems, which are investigated independently. This analytical approach suppose that properties as well as behavior of the whole system should be deduced from the properties of its subsystems. In systems biology, it is necessary to choose certain level of decomposition which leads to the key subsystem of interest reason. The other approach supposes that the complicated system is more then just the sum of its subsystems. This synthetic approach is the process of understanding how subsystems influence one another within a whole. Therefore, the system as a whole determines how the subsystems behave. However, living systems are complex functional wholes, which can produce surprisingly unexpected behavior. The stochasticity in the behavior arise from our inability to measure exact values of all system attributes with infinite accuracy on infinite range in infinite time. Unfortunately, the analytical and synthetic approaches had not gained corresponding position in the science.

Cellular behavior and cell fate estimators are the outputs which are expected from the systems biology in the near future. General mathematical systems theory is required in he systems biology to construct robust abstract models for experiments in silico. Interesting new paradigms of the systems theory were defined in the cybernetics in 1996 (Žampa). There was a demand for such a definition of an abstract system which would be sufficiently general as to cover any real problem and, at the same time, sufficiently specialized, as to enable to find an adequate physical realization to any theoretically given abstract system. This new systems theory fulfills also the conditions of living organisms, fortunately for systems biology.

Approach

Biology-inspired computational approaches such as neural networks or artificial life – agent based programming are only vaguely reflecting the information processing principles in biological systems. In case that we accept the description of fate of biological system as a movement in a chaotic attractor – in multifractal space. However the appropriate observable is a q-deformed entropy. This is reflected in measurable values – data points on microscope camera, nanoscope detected reflectivity and position changes etc.

Cell monolayer is the simplest model to organ function utilized in wide variety of applications. It is also closest approximation to the type of cell development which inspired the invention cellular automata in 1940´. Surprisingly, cellular automata are not the prevailing model approach in systems biology. Yet, they occasionally surface out unexpectedly in fields so distant as quantum mechanics (Blasone et Jizba).

Can we save cellular automata for biology or at least for objective description of cell monolayers? The time development of the cells may be described by stochastic cell automaton in which probabilities arise from the travel of systems variables in non-linear state space. The systems variables, as we propose as zero order hypothesis, are nothing else than metabolite fluxes in cell compartments as well as signal fluxes between the cells. Probability distributions for different fates of the cell (automata) are then given by properties of these underlying non-linear dynamic. Relations between cell fates and biological system variables may be mathematically treated as phenomenological attributes and system variables in engineering Stochastic systems theory (Žampa). In classical thermodynamics, the Gibbs (and/or Helmholtz) energy is the correct potential. Potentials represent a generalized property characterizing the sub-systems in equilibrium. In statistical physics it arise from maximization of Boltzmann-Shannon entropy under conditions of conserved energy, and number of particles. It is important to consider that Gibbs energy is unique value determined by all particles in the system. There may be many combinations of concentrations leading to the same Gibbs energy.

The information flux in dynamic systems whose system variables obey the non-linear dynamics rules at any time adopts available q-deformed entropy maximum. In another words, Renyi entropy maximum is the appropriate potential which enables to compare system states (Stys). Recent experiments (Cai et al, Choi et al) show that there is heterogeneity in molecule distribution among cells in the culture. Yet, all cells follow homogeneous fate. We propose that all cells in the culture represent multifractal objects whose Renyi entropy is (a) that of the respective cell culture – for cell cultures with no observable integration or (b) contributing to that of the cell monolayer.

In stochastic systems theory we define stochastic causal model which describes rules according to which system achieves values of phenomenological attributes. Internal variables of the model are system variables. Using the Blasone et al. terminology, there are observables and be-ables. The model is determined by time development of system variables. When the systems model is build, we have to determine time behavior of phenomenological attributes, and build models of system variables time behavior which is conform with observed phenomenological attributes development.

In reality, model trajectories must substantiate the multifractal character of the observed biological cell fate. The simplest model leading to chaotic dynamics is the pinball model with regions of asymptotically stable non-escaping periodic orbits. The geometry of the pinball leading of numerous stable trajectories consists of relatively dense structure of circles divided by free paths. The cell interior is also full of particles of different sizes and shapes which in most cases do not interact in a biochemical manner (i.e. complex formation or chemical reactions). Particles may well manifest stable trajectories from which they escape only occasionally to undergo biochemical interaction, namely transferring signal or chemical transformation. We thus propose the intracellular pinball model as working model for underlying mechanisms which lead to observed stochastic cellular automaton behavior of cell cultures. The intracellular pinball model naturally predicts numerous probability distributions.

Phenomenological attributes of cells are generally shapes and shape changes. Their relation to natural system

variables has always been difficult to explain. Recently a series of publications appeared which shows that cell-like 3D space partitioning naturally arises in the system of simplified discrete chemical reactions (Cybulski et al). We propose that in the dense mixture of compounds of non-negligible size arose set of stable states which corresponds to set of most probable states. The states have vast structural and chemical variability, yet until non-extensive entropy flux remains the same they contribute in the same way to system state.

Results and discussion

There are numerous experimental non-idealities in the time-lapse microscopy which can not be eliminated. Majority of alternative approaches requires sample modification (i.e. by fluorescent probe) which is often impossible in real life samples. We thus rather accept the experimental setup which is optimized for (a) least interference in the biological behavior of the sample and (b) maximum dynamic resolution of the camera. Actually, the sample image is captured each time with three different camera setups to increase the dynamic range. Properties of phenomenological attributes, i.e. intensities I all three RGB colour signals and at all three camera settings, are analysed by the operator which attributes them biological names and automatically by computer.

In manual analysis the operator becomes inevitably part of the system in the same sense as the equipment and analytical software. However, it still seems to be the only solution for many instances of cell biology. We made the meta-analysis of the system of cell culture development including the operator. Skilled biologist returns of course rather different dataset than the computer engineer. Yet, without manual analysis the macroscopic description of medically relevant cell cultures does not seem to be possible.

The phase contrast microscopy represents the observed object by the way of comparison of the refractivity index of the object (i.e. living cell) interior and refractivity index of free medium. As a result there is obtained image of light interference intensity in the focal point of the microscope. Refractivity index is a sum of non-absorptive, mainly electromagnetic, interactions of light with the matter. The objective assessment of the value of the refractivity index in the living cell interior is practically impossible using the phase contrast (Zernike). For the purpose of this discussion it is also important that the refractivity index is wavelength dependent. If the detection system is for example a standard photograph, each of the three channels (Red, Green and Blue) carries different, partly independent information, which may be used for state definition. The information carried by each of the data points at each channel represents the free energy of the cell interior with the degree of inadequacy comparable to that of one of the protein or ion concentrations observed in fluorescence microscopy (Zernike). For the analysis we propose that observed elements of the state trajectory are individual elements of the symbolic trajectory proposed by Vattay. By trajectory element we understand the ordered couple

$$(C(t, {}_{t,1}, {}_{t,2},\ldots, {}_{t,m}), D(t, {}_{t,1}, {}_{t,2},\ldots, {}_{t,n})) \qquad (1)$$

where $C(t, {}_{t,1}, {}_{t,2},\ldots, {}_{t,m})$ is complete immediate cause of the state $D(t, {}_{t,1}, {}_{t,2},\ldots, {}_{t,n})$ characterised by set of variables ${}_{t,1}, {}_{t,2},\ldots, {}_{t,n})$ The variables are not necessary concentrations. Quite the contrary. We may set the analogy with multiphase systems in thermodynamics: the system is equally characterized by size of droplets, surrounding medium etc. as by actual chemical concentration of all of the chemicals. However, when, as in most cases, the system is not in global minimum, the distribution of phases in given medium is more adequate approximation to the adequate

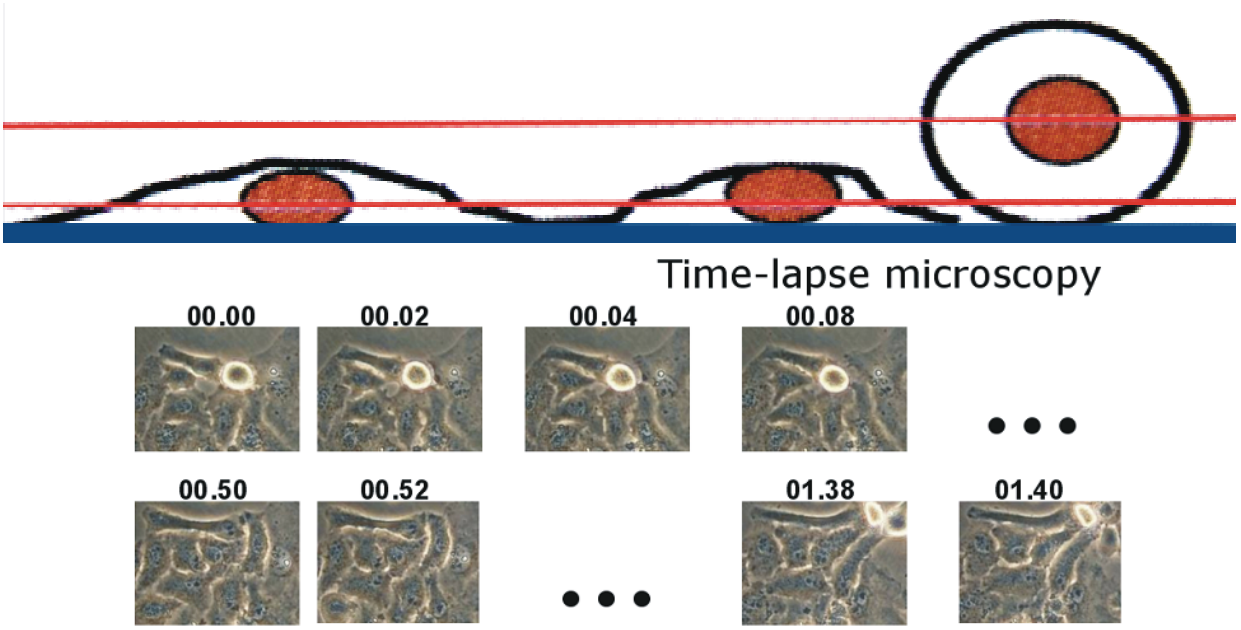

Figure 1. Upper part: Microscopic image represents only the layer within the focal plane and that unevenly. The *phenomenological attributes* have unknown relation to the distribution and optical properties of matter in the cell**. Lower part:** Time course of information content in a segment of time-lapse microgram. Time is denoted in hundreds of images.

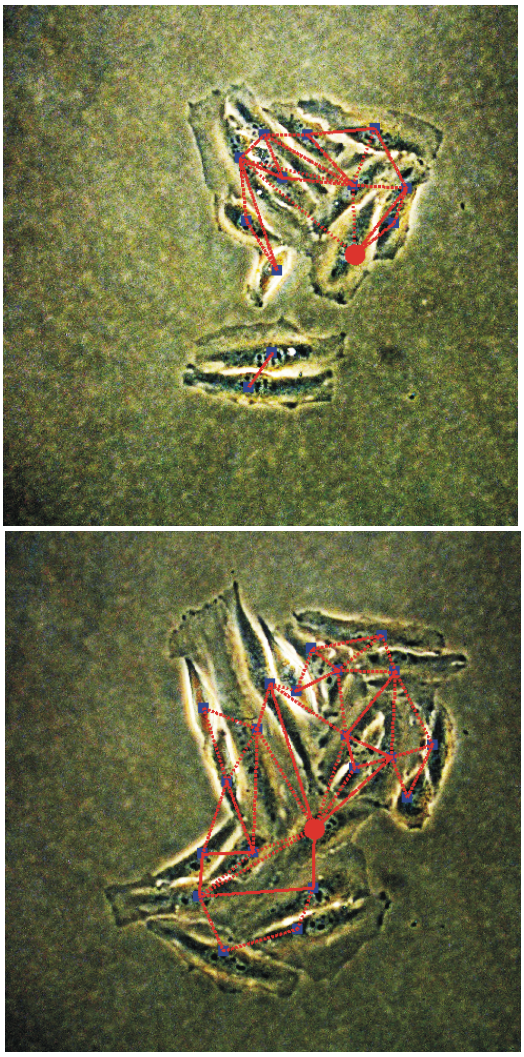

Figure 2. Cell monolayer culture image No. 1000 (999 min) and 2500 (2499 min) of the time-lapse experiment. The cell discussed in subsequent graphs is denoted by the red dot.

state function (i.e. Gibbs or Boltzmann energy) than precise knowledge of concentrations. Which are often determined in highly imprecise way, too.

Although theoretically apparently complex, the proposed method is essentially equivalent to biological intuition. Natural elements of the trajectory are elements of the cell cycle which have different names for different organisms. In the case of He-La cells mitosis and interphase. Naturally are observed events like cell death, cell fusion, anomalous cell division etc. The reality is that the manual analysis of the 3500 to 5000 images allows the operator to note only mitosis and interphase and notify the neighbourhood of newly appearing cells.

Figure 2 shows a dataset in the course of manual analysis and example of corresponding sub-graphs. The sub-graph showing fate of the cell followed from the point of view of the individual cell as system element (Fig. 3) is a reflection of the model according to which cells communicate only by direct long-term physical contacts. The cell fate itself and any change in number of its neighbours are noted. The sub-graph showing cell fate from the point of view of the whole system (Fig. 3) is an expanded version based on the assumption that any change in any cell is notified (i.e. through signal molecules) by all the cells. Detailed discussion would largely exceed the scope of this article.

From data obtained in this way, one may produce plot of length of these elementary trajectories versus experiment time (Fig. 4). The initial hypothesis was that there is certain "bounded asynchrony" in the cell development, as was proposed by Fisher et al. Since there was no guidance how to construct the model from the data, we decided to follow strictly the receipt of GSST. We assume that the system universum, the set of elementary sub-systems $_{i}$, , is formed by the set of all cells in the observed sample. The elementary sub-systems interact only by information bonds of the input or output type.

Sum of immediate input states plus internal development of sub-system (energetic and information development) creates complete immediate cause $C(C_{ext}, C_{\text{int}})$, where $C_{ext}(t, {}_{t,1}, {}_{t,2}, \ldots, {}_{t,m})$ and $C_{\text{int}}(t, {}_{t,m}, {}_{t,m\ 1}, \ldots, {}_{t,m\ n}, {}_{t,m\ n\ 1}, \ldots, {}_{s})$ of the state $D(t, {}_{t,s}, {}_{t,s\ 1}, \ldots, {}_{t,s\ x})$. This very general view is a framework defining parameters which we should search to define a trajectory element.

The analysis presented in fig. 2 shows the simplest approach consisting just of neighbouring cell counting – which splits the set C_{ext} into sub-sets C_j C_{ext} where n is number of neighbouring cells. And this is maximum information which the operator is physically able to record.

Let us discuss general definition of trajectory for this particular simplified case. Let us have set M representing all mitoses and I representing all interphases.

$$M \quad I \quad C, M \quad I \quad 0 \tag{2}$$

The relation $e({}_{1}, {}_{2})$ defined as

$$_{1} \quad {}^{t_1({}_{1})}_{l_1({}_{1})} \quad {}^{t_2({}_{1})}_{l_2({}_{1})} \quad {}^{t_1({}_{1})}_{} \ldots \quad {}^{t_i({}_{1})}_{l_i({}_{1})} \quad {}^{t_{i\ 1}({}_{1})}_{} \quad {}_{2}$$

where

${}_{1}, {}_{2}$ M and

$$i_1({}_{1}), i_2({}_{1}) \ldots i\ ({}_{1}) \quad I \tag{4}$$

where differs for each ${}_{1}$. Elements of C defined this way have unique identifier referred to as cell record and thus the seemingly complicated index structure is not correspondingly complicated in the computer implementation.

In biological terms ${}_{j+1}$ resp. ${}_{j+2}$ are daughter cell originating from the subsequent mitosis after ${}_{j}$ in one mother-daughter cell lineage, $i_1({}_{1}), i_2({}_{1}) \ldots i\ ({}_{1})$ are mutually different interphases occurring subsequently in the mother-daughter lineage defined by ${}_{j}$ and ${}_{j+1}$. (It should be noted here that notation ${}_{j}$ and ${}_{j+1}$ .is purely arbitrarily for the purpose of the derivation and correspond to unique cell identifier as it is introduced in Fig. 2)

This is sub-system j) for which we may define ordered sub-set

$$C({}_{i}) \quad \{ , i_1({}_{1}), i_2({}_{1}) \ldots i\ ({}_{1}) \} \tag{5}$$

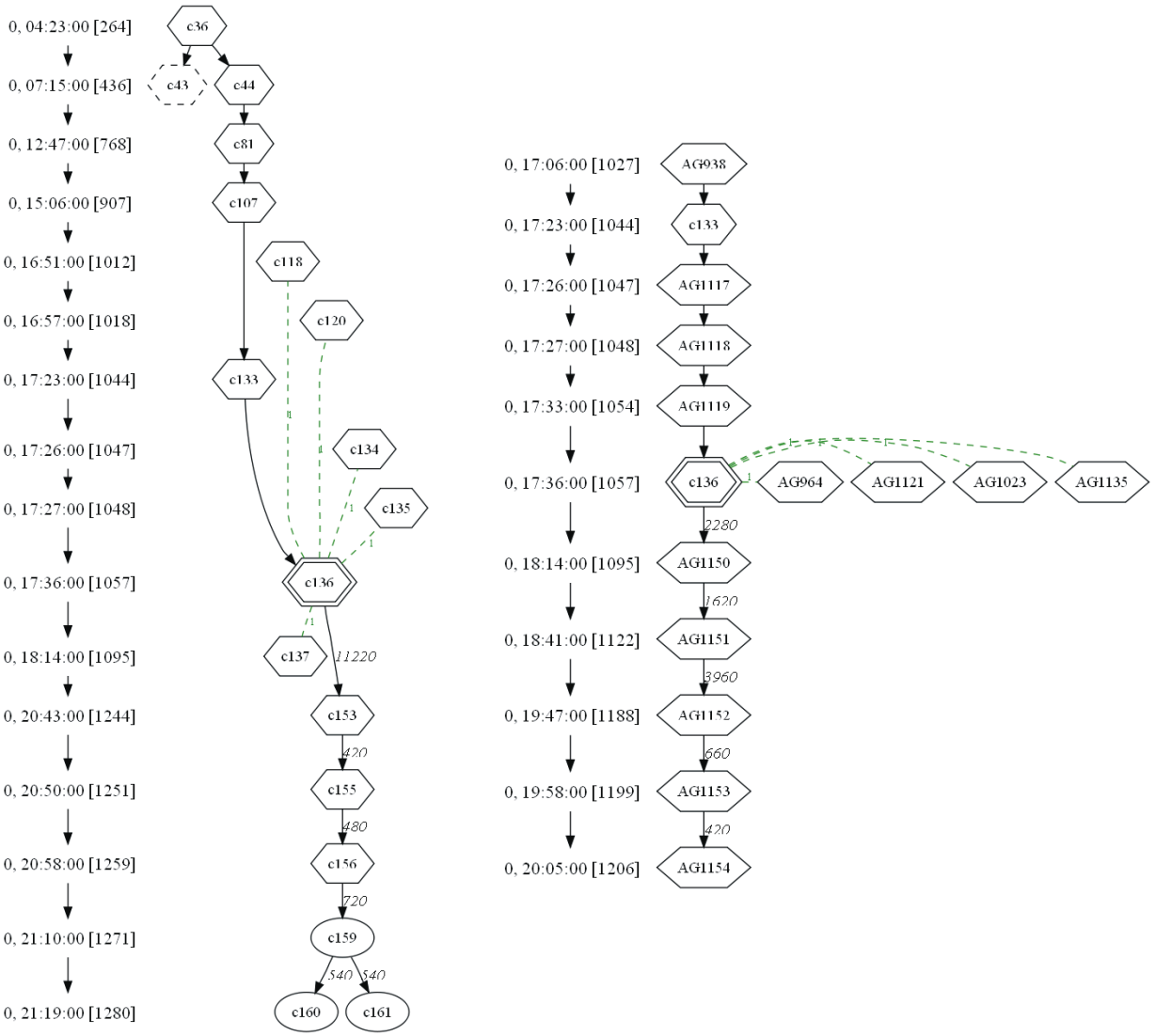

Figure 3. ***Left****:* Fate of the cell followed from the point of view of the individual cell as system element. Solid line represents one single cell fate, dashed lines represent cell neighbourhood. Complete information is depicted only for the marked cell. ***Right***: Cell fate from the point of view of the whole system. Cell numbering beginning with AG denotes automatically generated. Times of these AG cells represent any change in any cell in a particular neighbourhood network. By neighbourhood network we understand a cell cluster, all cells in contact either directly or mediated by other cell or cells.

where is number of different interphases between the mitoses in the particular lineag or states of the sub-sys - tem j). In other words $C(\ _i)$ is the ordered set of attributes of the sub-system . The number and identity of attributes is not known.

Time intervals $t_x(\ _j)\ \ 0, x\ \ 1,2,\ldots,\ \ 1$, form ordered set $_i$ as

$$(\ _i)\ \ \{t_1(\ _i), t_2(\ _i), \ldots, t\ (\ _i)\} \qquad (6)$$

Cartesian product

$$(\ _i)\ \ C(\ _i)\ \ (\ _i) \qquad (7)$$

for each $_j$ is called trajectory $(\ _j)$. It should be noted tha instead of representation of the experiment time by measurement time, we represent it by times between observable changes of attributes in any of the sub-systems of the system.

In the preceding three paragraphs we discussed definition of cell states. We defined on mitotic state and different states during the interphase. In reality, both within the mitosis and, namely, within interphase, there may be spotted different properties of the cell. They have to be mostly ignored in order to secure sensible time of the manual analysis. We assume that for the integration of the cell into the monolayer is most important cell-to-cell communication and that between neighbouring cells. Thus we decided to notify any change in the number of neighbouring cells. This is equivalent to assumption that each cell is a sub-system which has information bonds with geometrically neighbouring sub-systems. We then introduce a variable $_l\ _i$ where $= 0, 1, 2, \ldots,$ which represents the information bond to cells with which cells in the lineage of the mitotic cell $_i$ are in observable physical contact. The value $(\ _i)$ represents information bonds of the cell in mitotic state, values $(\ _i)$, $(\ _i), \ldots, (\ _i)$ represent all other dif-

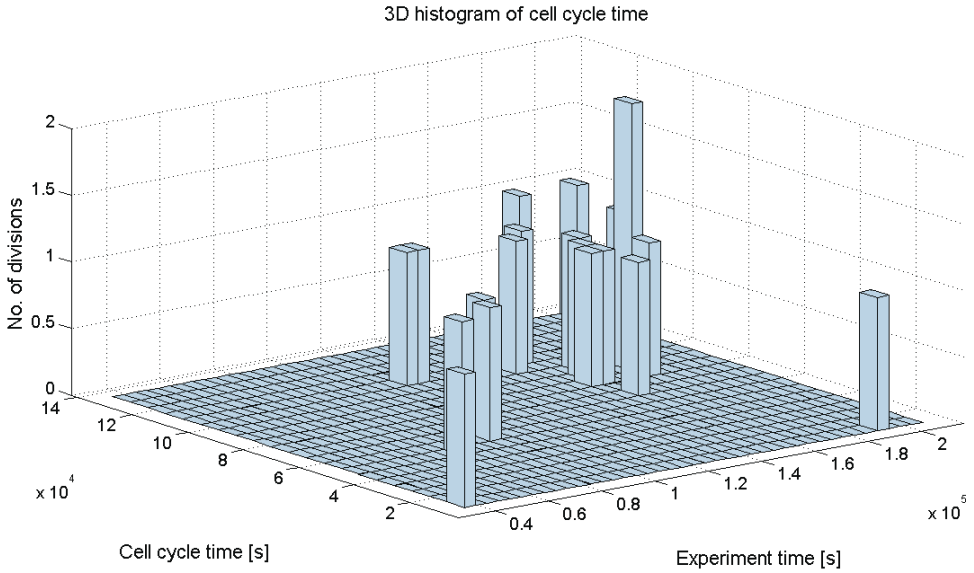

Figure 4. Dependency of cell cycle time on experiment time. Originally certain degree of synchronicity and uniformity of cell cycles was expected. However, this was not observed.

ferent information bonds. In another words, we consider $_{l}(\ _{i})$ the appropriate variable of the system.

For the purpose of further derivation we define

$$i_l^{\cdot}(\ _i)\quad i_k^{\cdot}(\ _i)\ \text{if}\ \ _l(\ _i)\quad\ _k(\ _i) \tag{8}$$

and may define ordered set $(\ _i)$ by

$$(\ _i)\quad\ _0(\ _i),\ _1(\ _i),\ldots,\quad(\ _i) \tag{9}$$

where we assume that for each $i_l^{\cdot}(\ _i)$ there is a i_1 in the set C. Precisely saying

$$C'\quad M\quad\{i_1^{\cdot}(\ _i)\ldots\} \tag{10}$$

for all $_i$ and observable $i_l^{\cdot}(\ _i)$. In other words

$$C'\quad C \tag{11}$$

and

$$'(\ _i)\quad\{t_0^{\cdot}(\ _i),t_1^{\cdot}(\ _i),\ldots,t\ (\ _i)\} \tag{12}$$

Where $t_l^{\cdot}(\ _i)$ is time at which was first observed corresponding $_l(\ _i)$.

We may then define real trajectory $'(\ _j)$ as Cartesian product

$$'(\ _i)\quad'(\ _i)\quad(\ _i) \tag{13}$$

and use it for further calculation.

$_l(\ _i)$ now contains all information about information bonds between the sub-systems. Let us denote the bond between two neighbouring cells $_{ij}$, or

$$_l(\ _i)\quad\{\ _{ij},\ _{ix},\ldots,\ _{iz}\} \tag{14}$$

where *j*, *x*, *z* may identify any cell record, i.e. any sub-system $_x$. $_{ij}$ itself does have three components: cell record 1 ($_j$ or $i_k^{\cdot}$), cell record 2 ($_j$ or $i_k^{\cdot}$) and order in which the bond was formed. Let us denote the order $=f,0$ or *l*. The identification of *f* and *l* we arbitrarily identify with cases when a new bond is formed due to change in the neighbourhood of the cell with the cell record 1($_j$ or $i_k^{\cdot}$), and *l* for the cases when the cell with cell record 1 ($_j$ or $i_k^{\cdot}$) creates a new bond due to change in geometry or mitosis. 0 is the case when divided mitotic cell inherits all neighbours from its mother. We may write for example

$$_{ij}\quad(\ _i,i_j^{\cdot},\ _{ij}) \tag{15}$$

This rather complicated definition allows us to discriminate between trajectories and propose framework for further analysis of the experiment. In the simplest approximation, we may overlook all different states of the cell in the interphase and characterize the sub-system $(\ _j)$, the mother-daughter following mitosis $_i$ cell lineage, only by time between two mitoses. This is the length of the cell cycle and is depicted in the Figure 3. As it is seen, there is no observable regularity in this dataset. This may be due to insufficient number of observation as well as due to inadequate representation of the trajectory.

In reality we have to work with available data. Already in the existent dataset there is substantial amount of information which is not generally used. For example, we may consider the trajectory $'(\ _i)$ or its sub-sets where only the set $(\ _i)$ is simplified, which leads to merge of certain $_{ij}$ $(\ _i,i_j^{\cdot},\ _{ij})$ and, consequently, to merge of certain $t_l^{\cdot}(\ _i)$. The use of maximum information contained in $'(\ _i)$ is schematically drawn in the figure 2.

Another approach is to consider the system in the whole. Which means to define global trajectory

$$'\bigcup_i\quad\ _i) \tag{16}$$

In this global trajectory contains information about all observable events in the system and their timing. in the system we may define system variables set

$$\bigcup_i (_i), \quad (17)$$

and new time set

$$' \cup '(_i) \quad (18)$$

With the assumption that the sub-system $(_j)$ is affected by all events in the system. For the definition of sub-system trajectory we may then write

$$_g^{'}(_j) \quad _g(_i) \quad _g^{'}(_i) \quad (19)$$

in which $_g(_i)$ are all observable changed combinations of attributes which were observed at all time instants $_g^{'}(_i)$ at which the particular sub-system $(_i)$ existed. This is schematically depicted in the figure 2.

Already these two simple approximation to system trajectory required substantial expansion of the dataset. In biological terminology all changes in the number of neighbours may be assigned to "newborn" cells (Figure 2). The neighbourhood was determined at each division, or to each of the "inherited neighbours" (Figure 2). This expansion brought us to the limit of index space.

Current substantial step forward brings information equivalent to those employed in the bound asynchrony model (Fisher). Instead of observing unique signalling pathways, which was possible in model organism C. elegans we propose observation of macroscopic states of neighbouring cells. This makes the method applicable to any cell culture, basically to any medicine or biotechnology practitioner.

In the course of the analysis we clearly observe other states of the culture, opening and closing of the intercellular channels and matter flux, formation of pseudopodia and matter transfer in non-neighbouring cells etc. These observations have never been considered in cell signalling based models for cell development. Further, for example the extent of the contact area between neighbouring cells may be a measure of probability and/or intensity of signal transduction. It has never been examined whether it is true although it is in principle simply measurable.

Real problem is that acquisition of this information by manual work of the operator is beyond her/his physical limit. It is not surprising that no model with substantial predictive power based on real life experimentally determined trajectories is available for mammalian tissue cultures. The automated analysis requires development of new methods which, equally well, are likely to be based on a stochastic (pseudo-)biological model. We propose to identify cells in the stage in which their margins may be easily identifiable (e.g. mitosis) and the evolution of cell borders will be followed similarly as in the analysis by the operator. This will enable quantification of cell properties - exact definition of cell states which are now covered under one common name etc. This is the first prerequisite for advance definition of cell monolayers state using, for example, thermodynamic formalism (Vattay).

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