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Life is change – dynamic modeling quantifies it

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The essence of life is change, as can be seen in processes as diverse as metabolism [1], beating of the heart [2], reproduction and evolution, or the thinking process of the human brain [3]. The patterns and rhythms of our lives are intrinsically linked to constant changes in our bodies and environments at all scales from the states of molecules, to cells, organs, organisms and entire ecosystems. Inanimate nature also undergoes change, obviously – it is considered after all to be the source of life – but there is a significant difference. Inanimate systems can attain a thermodynamic equilibrium and a sort of stasis. In the living world, the end of change means the end of life.

Science aims to capture an impression of change, to measure it, record it or scientifically formulate it. However, all the experimental tools and devices we have to do so capture merely snapshots of the state of a system at a moment in time. Even the fastest high-speed cameras record a series of snapshots, and it is only through the neuronal processing underlying human vision that we experience the sequence of snapshots as continuous change much like a movie. Hence, all our measurements and videos show sequences of states, not the changes themselves. A simple example such as a moving body illustrates the challenge of capturing dynamics: What changes is the position of the object. Looking at a specific position, the object is for some length of time not yet there or already past it. Only for a point in time it actually occupies this position. So how can we draw value from the snapshots we measure, if they are valid only for a moment? We do so only by assuming that the snapshots are connected by a continuous transition.

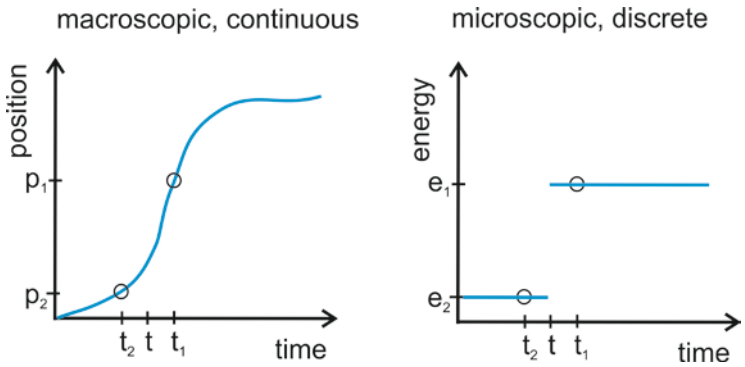

Figure 1 Derivatives quantify change, if they exist. The macroscopic example shows the position during motion. The position at time t_1 is p_1, analogously p_2. To capture change, we calculate $(p_1-p_2)/(t_1-t_2)$. If we choose both t_1 and t_2 closer to t, the difference t_1-t_2 approaches 0. So does p_1-p_2. The ratio $(p_1-p_2)/(t_1-t_2)$ attains a value which we call the derivative of the position. It is equal to the velocity at time t. Excitation energy levels of an electron in an atom represent the microscopic example. The transition from e_1 to e_2 happens at time t. Here again, t_1-t_2 approaches 0, if we move both t_1 and t_2 closer to t. However, e_1-e_2 stays finite and does not approach 0. The value of $(e_1-e_2)/(t_1-t_2)$ diverges to infinity. We conclude that the derivative does not exist.

When we deduce a continuous time course of observables from our sequence of snapshots, we can draw confidence (in a reflection of our systems behaviour) from mathematics. The mathematical formulation of change starts from our ability to record snapshots, or in our example, positions. It determines the difference of two positions in relation to the difference points in time at which these positions were measured (see Figure 1). The ingenious step of abstraction accomplished by differential calculus (I. Newton, G.W. Leibniz late 17th century, A.-L. Cauchy early 19th century) was to

decrease the increment of time between the measurements towards 0, which turns the ratio of the differences into the derivative of the position with respect to time [4]. Differential calculus provided us with a quantitative scientific definition of change and created classical mechanics - a theory revealing the mathematical structure behind mechanical observations, and a theory with thus far unprecedented explanatory power.

This calculus enables us also to predict all later states of a system if we know its state at one moment in time [5]. This predictability follows from the existence of derivatives (see Fig. 1) [5]. Measurable quantities of *macroscopic* objects like position or temperature change continuously and hence, their time derivatives exist and the time course of their states can be predicted [6].

Microscopic objects such as molecules or small groups of molecules don't behave this way. They jump between states that are assigned discrete values, like `open' or 'closed' for ion channels or different levels of excitation for electrons in molecules [7]. Derivatives do not exist at the time of the transition (Fig. 1). Neither is the state of microscopic objects predictable. They are in a specific state with some probability but not with predictable certainty [7]. Notably, the time derivatives of these probabilities exist in the microscopic world, and their values can be predicted [8]. Thus, mathematics captures change either as differential equations for the state of macroscopic objects or as stochastic process in the case of microscopic ones.

The lack of certainty on the state of a microscopic object involves frequent changes of state. Indeed, a single molecule in a solution changes its state, position or velocity incessantly due to interactions with all the other molecules in its vicinity. The resulting fast random dynamics has the molecules explore the whole range of states compatible with the macroscopic properties of the solution – all positions, velocities, energy levels etc. [7,8]. This exploration of all possible microscopic states is called ergodicity [7,8]. At the same time, the emerging macroscopic properties like temperature and concentrations change much more slowly or remain constant [8].

Large ensembles of molecules and individual ones have different relationships to time. The change of state in time can be predicted for macroscopic objects, but not for microscopic ones. There is something of a parallel in cultural history: A paradigm shift in the self-perception of humans from 'one of many in an ensemble' to 'many unique individuals' (the emergence of personality) coincides with a similar radically new perception of time. The perception of time expressed in early religions was cyclic – day, year, life span. There was neither history nor development. At the same time, human beings were considered as one of many. These religions did not assume that the individual is noticed as such by the deity, and consequently individuality or personality was not a value in itself. Judaism established the direct dialogue between the Jewish god and each individual human being. The person was noticed as such by god, individuality became a value. At the same time, Judaism broke out of the cyclic view on time and changed its perception to a directed history with a beginning and an endpoint. The discovery of the individual changed the perception of time as the discovery of the microscopic world changed scientific ideas on dynamics.

Box 1: A feuilleton on time and individuality.

We have dedicated this issue of ‚Current Opinion in Systems Biology' to the dynamic mathematical modelling in the life sciences since dynamics are intrinsic to life, and the differential equations and stochastic processes used by mathematical models are their only quantitative formulation. Dynamic

modelling has been successfully applied to biological concepts on all structural levels. In some examples, dynamic theory has been pivotal in understanding of processes of life or has predicted the outcome of experiments.

Modelling is particularly useful for spatio-temporal processes like cell polarization and waves. Complex patterns formed through waves – like e.g. rotating spirals – can be only explained by dynamic theory [9-14]. They occur as the propagation of a specific state. Examples are the depolarized state of the membrane potential during propagation of action potentials along axons [13,14], an increase of the cAMP concentration spreading through populations of Dictyostelium discoideum [12], a range of high cytosolic Ca^{2+} concentration travelling inside cells like oocytes [11,15], hepatocytes, myocytes and others and even intercellularly in astrocyte networks, epithelia, liver and during development [16,17]. The contribution by Rappel and Edelstein-Keshet illustrates the state of modelling of cell polarization as one example of a spatio-temporal phenomenon [18].

Dynamic modelling is mandatory for oscillatory, repetitive irregular or chaotic behaviour. Empirical experimental methods can identify components of the system but only mathematical models allow establishment of the conditions required for oscillations. The most spectacular examples have been presented in the field of neurobiology. The action potential of single neurons may consist of sequences of depolarization spikes, bursts with a variety of internal dynamics [19-21] or even chaotic behaviour [22]. Dynamic theory provided a classification and systematic understanding of these firing patterns in terms of bifurcations of stationary states and limit cycles.

Two classical systems of modelling in cell biology are represented by intracellular Ca^{2+} dynamics and p53 oscillations. New ideas of specifying their dynamics have recently been published [23-25]. In both cases, modelling has matured to generating hypotheses and suggesting experiments pivotal for mechanistic understanding. In both cases, noise is at the centre of discussion at present. Repetitive pulses may occur due to oscillatory dynamics or due to an excitable regime with repeated noise initiating spikes. While the difference in the time courses of the pulsing concentration may appear of little significance, the difference of predicted parameter dependencies between the two mathematical assumptions is substantial. The contributions by Sneyd and Dupont [26] and Batchelor and Loewer [27] review the state of modelling for these two systems. Martinez-Corral and Garcia-Ojalvo present a review on how this pulsatile signalling controls its effectors [28].

Mathemtical models are a means to integrate data from different sources and experiments. At the same time, they can be formulated in a modular and iterative way and thus in the end capture very complex systems and problems. Kirschner et al. review such an approach for disease modelling, specifically M. tuberculosis (Kirschner et al.).

Frequently, mathematical models provided the concept for understanding cell behaviour and complex data. One of the most successful concepts was the prediction of ultrasensitivity by Goldbeter and Koshland [29]. They discovered a principle that applies to many binary biological processes and helps decision-making processes for example on cell fate or metabolic states. This general principle has been experimentally confirmed in many contexts by now.

What are the current challenges of dynamic modelling? I would like to mention here only two fields of research: (the growing number of layers of) gene transcription and translation regulation and cell-to-cell variability. Their conceptual importance to biology is self-evident. It seems likely that they will also gain conceptual importance to biology's mathematical formulation, since recent data indicate

that the relation between erratic single cell behaviour and reliable organ function mirrors the powerful concepts from statistical physics we have mentioned above.

In terms of dynamical systems theory, the state of each cell can be characterized by a point in a coordinate system the axes of which represent the dynamic variables like concentrations, volume, membrane potential, etc. The coordinate system spanned by all dynamical variables is called phase space. Each cell type (and their states like cancerous, senescent, …) defines an attractor, which is a sub-region of the phase space comprising the values actually realized by cellular dynamics [30,31]. This is the basis of Waddington's landscape concept [32] in mathematical terms. Given the combinatorial complexity of the genome of a species together with the nonlinear dynamics of cellular processes, the number of possible attractors for a given cell would be so large that reliable selection of a specific attractor – being a specific cell state or cell type – appears unlikely. Epigenetics taught us that most of the time the majority of all possible combinations are not realized. That separates cell states from each other with respect to the expressed and functional proteome and thus renders them unique and distinguishable. In some cases, distinction of cell states might be difficult due to frequent differentiation process [33] and epigenetic heterogeneity [34]. But the questions are now: Can we identify attractors/cell states with epigenetic states, or do epigenetic states in general allow for several attractors [30,35-37]? Dynamic systems theory allows for both possibilities, but in the former case understanding state changes would be identical with understanding the change of epigenetic states. This is a current challenge for epigenetic modelling. The contribution by Ringrose and Howard reviews modelling of epigenetic and gene regulatory processes involved in these dynamics [38].

The same concept also offers a new angle on understanding differentiation. We know from dynamic theory that several attractors may coexist under the same environmental conditions. Switching between these attractors may occur along different trajectories in phase space, some more likely than others, but does not require a specific pathway. It thus accounts for basic observations in cell biology like redundancy of pathways or processes, and multifactorial causalities [36]. The switch may be caused by noise (biochemical, transcriptional, etc.) or transient changes of relevant parameters [39-42]. Of course, this includes state changes due to regulation through signalling pathways and other more targeted processes (i.e. rather bifurcations in mathematical terms). The contribution by Jolly and Levine reviews modelling in that context, specifically modelling of the epithelial-mesenchymal transition.

Cell-to-cell variability is a basic observation in each lab, but despite its ubiquity it has gained attention only recently with the advent of single cell biology. Variability is substantial with respect to the proteome [43,44], the transcriptome[44], signalling [23,45] and function [46,47]. Starting from a functional man made engineering design, function would be lost, if we increase or decrease the number of its components in an unrelated way by a factor of 2. However, this is less than the proteomic variability we find in cells [30,43,44]. Given such a great variability on the level of the cell's proteome, what are the design principles functional cells obey? It will probably take a while until we understand the underlying principles. However, we can start right now to use observed variability as a selection criterion for models.

It appears to be sensible to relate cell variability to the attractor concept. The range of variability corresponds to the extension of cell state attractors in phase space in this view. Experimental exploration of these ideas revealed that individual cells do not occupy a single fixed point but move

about the attractor belonging to their cell state [30,35,39,40]. Hence, cell variability is not a static phenomenon. This is very evocative of ergodicity and indeed, this concept has been linked to these observations [44]. Ergodicity comes along with unpredictability of the microscopic states – the cell state in our case. Will we gain major insights trying to understand the state of a single cell? Or do we not rather reach predictable results by looking at the property of the attractor confining single cell behaviour?

How do attractors become tangible or observable? Cell variability offers an easily accessible way of exploring attractor properties. In each experiment recording single cell data, we get as many records of single cell behaviour as there are cells in the experiment. Relating a dynamic property of each cell to another property of the same cell reveals attractor features. If these dynamic properties are protein concentrations [30], we directly obtain a map of parts of the attractor in the concentration space [30]. Thus protein concentration distributions are a macroscopic characterization of attractors [35]. The contribution by Komin and Skupin elaborates on this idea.

Mapping the attractor on the molecular level is experimentally elaborate. We can also choose an easier approach. The existence of an attractor is equivalent to the existence of *algebraic* relations between protein concentrations or other dynamic variables describing cell behaviour. These dynamic variables include functional or operational properties like spike frequencies in neurons or cell velocities of motile cells. If we find an algebraic relation between them, we have found a property defining the attractor (see e.g. [23] for an example from signalling or [47] from cell mechanics). This relation is at the same time an operational rule or input-output relation of the cell.

In the long term, the task of mathematical modelling is to turn biology into a more quantitative science. This requires concepts as general as possible from which we can derive equations describing cell behaviour, and it requires mathematical properties to become part of the definitions of cell types and basic observations. These quantitative definitions have to account for variability. The attractor concept and the operational relations and distributions defined by attractors may become a quantitative definition of the cell type, pathway or cellular subsystem accommodating cell variability (see e.g. the Eqs. (1, 2) in[23] or Figure 4 in [47]).

These are fascinating times with respect to the appearance of mathematically motivated concepts for biology. The teaser in box 1 relates intellectual history to how we might experience them: Individuality and the perception of progress are related and individuals change faster than society. Many individual labs have picked up these concepts already and put them to the test. It will require more individual efforts to verify their applicability and - if successful - to reveal their potential to turn cell biology into a much more quantitative science.

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