ENERGY IS THE MAIN PARAMETER IN ALL STAGES OF DRUG DEVELOPMENT

PREFACE

When I got engaged in the algorithm building for automated detection of behaviours, it was obvious for me that the matter is random signal (in this case animal behaviour). Logically I asked the most important question of how can I find generalities in the same behaviour at different points of time. It was necessary to understand thoroughly the concept in order to create the mathematical model, and then build an algorithm which will detect the behaviour. I have arrived at an interesting conclusion after extensive statistics tabulation and analysis of Laboras signals as well as after the studies of the behaviours of rats and mice. I have studied the entire process of drug development; this helped me to find out the important links between the stages of drug production.

The new algorithm for the automated behaviour detection by Laboras system assumes great responsibility for us. Laboras system is used in drug development studies. Then these new drugs are put on the market all of us are using those drugs. The effectiveness of the drug greatly depends on the success of equipments and experiment results.

The main stages of drug production are:

- Molecular biology
- Biological systems(cells, reticulum)
- Preclinical research
- Clinical research

When the drug penetrates into the organism, a biochemical reaction takes place and one can say the latter produces energetic changes in the organisms of the laboratory animals. The drug penetrating into the organism changes the potential energy of the body; the latter after some time brings to changes in kinetic energy which is expressed in people and in animals as changes in behaviour. This means that energy is the most important parameter in all stages beginning from molecular biology to preclinical research. After thorough studies of all stages I came to the conclusion which was proved by the statistics and analysis of algorithm for Laboras system that energy or any variable depending upon is of great interest in all stages. And researchers can achieve success only through a team work. I think medical science is not to be viewed as a separate science: medical science can be generalized with all natural sciences. Therefore in drug production we have to do with many branches of science such as molecular biology, biochemistry, physiologic chemistry, biological systems, biology, chemistry, physics, nuclear and atomic physics, mechanics, thermodynamics, and mathematics.
I think that development and production of new drugs will achieve great results if

- The problem is solved through teamwork involving specialists from different branches of science
- Precision tools are used in all stages of development
- Precise definitions are given in all stages
- Different parameters are to be defined accurately, the group of which will yield in high results
- All testing stages are implemented completely and minimum testing criteria are defined

HISTORY

Adam P. Arkin, an assistant professor of chemistry and bioengineering at the University of California considers computation to be the practical application of theory, but he believes that experimental data are necessary to keep theory realistic. "The thing about theory and computation is that they are very compelling until an experiment is done," he says. "A theorist who is constantly generating theory without experimental feedback is in danger of migrating away from reality, especially in biology and pharmacology."

Christophe H. Schilling, vice president and chief technology officer at Genomatica in San Diego also believes that a combination of computation and experiment is vital. "If you generate a model in a vacuum and don't make a prediction that you can then test, you don't know if a model is right or wrong," he says. "If you generate data without a hypothesis, in some respects you can prove anything you want. Mathematical models, if you do them right, become hypotheses that are testable." For properly the build a new model, you need right definitions. Schneider advocates borrowing methods from engineers, particularly from electrical and chemical engineering. "The key is the unit-operation approach. You have to define the physiological unit operations," he says. "On a fundamental basis, there's really nothing different between unit operations for resistors, capacitors, and induction coils than for Michaelis-Menten kinetics, membrane transport, and chemical equilibria. They're just equations that apply."

One challenge of modeling biological systems is that most biological data are "differential display" data, dealing with changes between states. "It's not measuring an absolute level," Schneider says. "This is where we went back into chemical engineering and process control theory and figured out you can do some really nifty linear algebra. Then you don't have to worry about absolute numbers anymore. This linear algebra trick took us out of having to do numerical integration into doing algebra problems."

Because of its many facets, Drugs development attracts scientists from a variety of disciplines, including the basic sciences, engineering, and computer science. ," Leroy E. Hood, cofounder and president of the Seattle-based Institute for Systems Biology sees the field as needing "the integration of a cross-disciplinary group of scientists working together." In fact, he believes that future scientists will have to become familiar with multiple subjects.

"All biologists should really think in terms of two subjects," Hood says. "If you're a biologist, you should also think about computer science or applied mathematics or engineering. I think everybody ought to learn biology, plus either a quantitative computational skill or a physical skill. I'm very much attracted to a dual mentorship idea."

Arkin's group, which includes 33 people from 12 departments and five institutions, exemplifies the multidisciplinary nature of systems biology. "They're very diverse, and they're forced to hang out together," he says. "For four to six years, they're in a laboratory in which there are people who are mechanical engineers, bioengineers, chemical engineers, physicists, biologists, mathematicians, statisticians. They learn the language, but each one is trained in his or her own department."

AstraZeneca's Fickett points out that most of what is known about protein interactions is contained not in databases or mathematical equations but in the text of the scientific literature. "We want to figure out how to get that information out of the literature and into the hands of our scientists when they're trying to make decisions about which direction to take with a drug discovery program," he says. "We're doing quite a bit of work on categorizing scientific articles according to what molecular processes might be discussed in the text."

Entelos also focuses on modeling, taking what Paterson calls a "top-down" approach. "We start with the high-level system phenomenon and work down," he says. "The end point that we care about is not a protein-protein interaction. It's not even how a cell behaves in culture. It's how the integrated human system is going to behave." Entelos wants to understand the clinical end points of disease.

The challenges associated with the top-down approach are the same as those in reverse engineering, according to Paterson. In particular, there are often going to be gaps in the knowledge of the system.

"We're very much driven by mapping out what we don't know," Paterson says. "In the areas that we don't know things, where we have knowledge gaps, we have a systematic procedure where we formulate multiple competing hypotheses and then test those hypotheses mathematically to see if they are consistent with the overall data. In many cases, it allows us to triangulate on the right answer."

Paterson believes the top-down approach is particularly suited to modeling complicated diseases. "When you have phenomena at the clinical level that are very complex, that gives us a large number of constraints that are valuable for helping us to reverse engineer those knowledge gaps where we don't have a lot of understanding," he says. Entelos is constructing models for diseases such as asthma and diabetes.

Systems Biology has the potential to impact a wide range of biological research. For example, the Department of Energy has started a program called Genomes to Life, which emphasizes systems biology. The program will focus on applications in environmental cleanup and new energy sources.

In another approach, Genomatica focuses on modeling metabolism, which is the process by which cells gain energy for all other functions. "We feel that metabolism offers a logical starting point for the development of complete cellular models and also complete holistic models of multicellular organisms or whole-body models," Schilling says.

The company takes a "constraints-based" approach to metabolism. "The emphasis is on trying to place constraints on metabolism based on physical and chemical laws that govern all systems," such as conservation of mass or energy, Schilling says. These are considered "hard" constraints because they apply equally to all systems. Additional system-specific constraints are provided by the repertoire of reactions that an organism's genome makes available to it. "Based on the limitations of what reactions are available, the stoichiometry of those reactions, and the thermodynamics associated with the reactions, we can further limit what's possible by the cell and by metabolism," he says. Genomatica has concentrated on microbes such as *E. coli* and yeast. The models can be used to predict the performance of an optimally designed microbial strain. Genomatica researchers have found they can use selective pressure to force the organisms to evolve to reach the optimal state, which could have uses in designing microbial strains for bioprocessing and in finding ways to overcome antibiotic resistance.

Unlike many other systems biology companies, Beyond Genomics in Waltham, Mass., is emphasizing the experimental aspects. "I view Beyond Genomics' systems biology as an outgrowth of measurement technologies with a sophisticated overlay of bioinformatics," says Robert N. McBurney, senior vice president for research and development and chief scientific officer. "The in silico stuff is the back end. If you don't have a good biological or clinical experimental design, the back end is completely useless. If you don't have high-quality samples, the back end is useless. If you don't really know what you're doing with your instruments, the back end is useless. I think Beyond Genomics' strength is that we're not an in silico shop."

Systems Biology has the potential to impact the entire drug discovery and development timeline.

"I think systems biology will affect everything we do," Fickett says. "In the context of drug discovery, it's about the connection between the molecular and the physiological. When people look back at these decades from a later viewpoint, they'll see that this was the time when molecular physiology really took off.

For example, biomarkers for efficacy and toxicology could lead to more efficient preclinical development. Beyond Genomics is integrating proteomics and metabolomics to find surrogate markers for efficacy and toxicology. "I would say there are more diseases for which we have no surrogate measures for drug efficacy than there are diseases like atherosclerosis, for which we have cholesterol," McBurney says.

"When a lot of the first '-omic' technologies came out, one felt that by understanding the gene or the genes that were involved in a disease, you essentially had the way paved for identifying better, safer, more effective targets for drug discovery," says Thomas Colatsky, vice president for health care research at Paradigm Genetics in

Research Triangle Park, N.C. "There's been a growing awareness that some of the same risks that always existed in drug discovery and development still exist. The systems biology approach puts all that information in the context of what happens to the entire organism."

"Not only will you identify a disease target to start your drug discovery efforts, but that target will be put in biological context," Schneider says. "You'll understand the pathway it's involved in. You'll understand the metabolic fluxes through that pathway and how they're altered in the disease state. And you'll have a mathematical model you can use as a predictive tool."

Paterson hopes that systems biology will help the pharmaceutical industry become more like other R&D-intensive industries, such as the aerospace, automotive, and electronics industries. "They make good use of simulation technologies before they actually build costly prototypes, the equivalent of going to a clinical trial," he says. In contrast, he says, pharmaceutical companies often have only their hypotheses about human efficacy to guide them before Phase II clinical trials, making a large portion of the process trial and error.

"The aerospace and automotive industries abandoned trial and error a long time ago. By the time they actually get to driving a prototype, it's all confirmatory," Paterson says. "In the pharmaceutical industry, the cumulative failure rate past Phase I is almost 75%. Even after toxicology in Phase I, 75% of the time the hypothesis about how the drug is going to affect clinical end points is wrong. I see the biggest impact that systems biology is going to have is in fundamentally changing the success rate in clinical trials, particularly Phase II and beyond."

MOLECULAR BIOLOGY

Molecular biology is the study of biology at a molecular level. The field overlaps with other areas of biology and chemistry, particularly genetics and biochemistry. Molecular biology chiefly concerns itself with understanding the interactions between the various systems of a cell, including the interactions between DNA, RNA and protein biosynthesis and learning how these interactions are regulated.

In this stage the researchers are conducting experiments using different substances, and during experiments the processes are going on with energetic changes, the latter tries to keep the energetic balance of the system. Of course one can assume that energetic fluctuations in molecular stage will cause energetic changes in the next stage, i.e. between the cells in biological systems.

Molecular modelling is a collective term that refers to theoretical methods and computational techniques to model or mimic the behaviour of molecules. The techniques are used in the fields of computational chemistry, computational biology and materials science for studying molecular systems ranging from small chemical systems to large biological molecules and material assemblies. The simplest calculations can be performed by hand, but inevitably computers are required to perform molecular modelling of any reasonably sized system. The common feature of

molecular modelling techniques is the atomistic level description of the molecular systems; the lowest level of information is individual atoms (or a small group of atoms). This is in contrast to quantum chemistry (also known as electronic structure calculations) where electrons are considered explicitly. The benefit of molecular modelling is that it reduces the complexity of the system, allowing many more particles (atoms) to be considered during simulations.

Molecular mechanics is one aspect of molecular modelling, as it is refers to the use of classical mechanics/Newtonian mechanics to describe the physical basis behind the models. Molecular models typically describe atoms (nucleus and electrons collectively) as point charges with an associated mass. The interactions between neighbouring atoms are described by spring-like interactions (representing chemical bonds) and van der Waals forces. The Lennard-Jones potential is commonly used to describe van der Waals forces. The electrostatic interactions are computed based on Coulomb's law. Atoms are assigned coordinates in Cartesian space or in internal coordinates, and can also be assigned velocities in dynamical simulations. The atomic velocities are related to the temperature of the system, a macroscopic quantity. The collective mathematical expression is known as a potential function and is related to the system internal energy (U), a thermodynamic quantity equal to the sum of potential and kinetic energies. Methods which minimize the potential energy are known as energy minimization techniques (e.g., steepest descent and conjugate gradient), while methods that model the behaviour of the system with propagation of time are known as molecular dynamics.

$$E = E_{bonds} + E_{angle} + E_{dihedral} + E_{non-bonded}$$

$$E_{non-bonded} = E_{electrostatic} + E_{vanderWaals}$$

This function, referred to as a potential function, computes the molecular potential energy as a sum of energy terms that describe the deviation of bond lengths, bond angles and torsion angles away from equilibrium values, plus terms for non-bonded pairs of atoms describing van der Waals and electrostatic interactions. The set of parameters consisting of equilibrium bond lengths, bond angles, partial charge values, force constants and van der Waals parameters are collectively known as a force field. Different implementations of molecular mechanics use slightly different mathematical expressions, and therefore, different constants for the potential function. The common force fields in use today have been developed by using high level quantum calculations and/or fitting to experimental data. The technique known as energy minimization is used to find positions of zero gradient for all atoms, in other words, a local energy minimum.

Lower energy states are more stable and are commonly investigated because of their role in chemical and biological processes. A molecular dynamics simulation, on the other hand, computes the behaviour of a system as a function of time.

It involves solving Newton's laws of motion, principally the second law, **F = ma**. Integration of Newton's laws of motion, using different integration algorithms, leads to atomic trajectories in space and time. The force on an atom is defined as the negative gradient of the potential energy function. The energy minimization technique is useful for obtaining a static picture for comparing between states of similar

systems, while molecular dynamics provides information about the dynamic processes with the intrinsic inclusion of temperature effects.

Molecular modelling methods are now routinely used to investigate the structure, dynamics and thermodynamics of inorganic, biological, and polymeric systems. The types of biological activity that have been investigated using molecular modelling include protein folding, enzyme catalysis, protein stability, conformational changes associated with biomolecular function, and molecular recognition of proteins, DNA, and membrane complexes.

Molecular Logic Table

Topics in Biology	**Underlying Molecular Phenomenon**	**Molecular Logic: How molecules behave**	**Variables**	**Models Available**
Introduction How molecules behave --------- Energy	Molecular Kinetic motion -------- Energy	Molecules move, collide, exchange energy; Heat and Temperature; gas-liquid-solids: phase change and distance between particles ---------- Energy	Rat or mice, concentration, temperature, pressure, collisions,distance ---------- Energy	MW: Atoms in Motion -------- Energy

Systems Biology

Integrative approach in which scientists study pathways and networks will touch all areas of biology, including drug discovery.It's different from molecular biology, which only studies the molecules. It's the phase in-between.The past decade has seen the ascendance of high-throughput methods for measuring the global expression of different components of the biological landscape--genomics, proteomics, metabolomics. These "-omics" often stand in isolation. But the time has come to pull them together to gain an understanding of biology at a higher level, with its complex collection of networks and pathways.

Christophe H. Schilling, vice president and chief technology officer at Genomatica in San Diego, agrees that the idea of systems biology is not new. As he worked on his doctoral thesis, he found that "people had talked about systems biology for quite

some time," he says. "I think the difference is that it hasn't been until recently that we've had the experimental tools available to begin to look at biological systems."Those experimental tools, Schilling believes, have forced people to take a systems approach. "If you're faced with looking at a microarray with thousands of genes on it, it's a pretty harsh reality to look at that and understand that those are a thousand components that are all working together inside a cell."

Tongue in cheek, Adam P. Arkin, an assistant professor of chemistry and bioengineering at the University of California, Berkeley, and a scientist at Lawrence Berkeley National Laboratory, claims that there's no such thing as systems biology. "Being one of the major proponents of it, I can safely say it doesn't exist," he jokes. "I think I can say that because what people mean by this is what people have always done in biology, which is physiology of cells."

Hans V. Westerhoff, a professor of microbial physiology at Free University in Amsterdam, takes a slightly contrarian view. "Systems biology is not the biology of systems," he emphasizes. Instead, he says, it is the region between the individual components and the system, which is why it's new. "It's those new properties that arise when you go from the molecule to the system," he says. "It's different from physiology or holism, which study the entire system. It's different from reductionist things like molecular biology, which only studies the molecules. It's the in-between."

Pre Clinical

Measuring animal behaviour under laboratory conditions – Laboras system

Steps in the construction of an animal model

1	Drug X has a behavioural effect in humans that resembles human pathology e.g. drug X produces depression when given to humans
2	Drug X produces similar behavioural effects in animals, allowing for any species differences in behaviour
3	Drug X produces specific biochemical effects in animals
4	Thus the biochemical effects produced in animals provide data relevant to the behavioural effect of drug X in humans
5	If the behavioural effect of drug X in humans has the same characteristics as pathological behaviour, then the biochemical changes produced by drug X in animals may also provide data relevant for the understanding of the abnormal human behaviour.

Measuring animal behaviour under laboratory conditions – Laboras system
An area of psychology called psychopharmacology or behavioural pharmacology is concerned with measuring the effects of drugs on behaviour. Exploring the effects of drugs on operant schedules of reinforcement has a long tradition in psychopharmacology. Here is some of the technology used by psychopharmacologists.

A model is a simple representation of a complex system. For example, a model aeroplane or train looks similar to the real thing but lacks all the features of the full size object. An animal model of a psychiatric disorder is an attempt to capture the essence of the condition, but it does not claim to reproduce the human condition in

an animal. Depression, schizophrenia and anxiety are probably uniquely human conditions. One purpose of an animal model is to discover novel medicines that combat the abnormal behaviour in the animal model which could be then be used to alleviate human suffering.

Read Barrett and Miczek (2000) Behavioral Techniques in Preclinical Neuropsychopharmacology Research which is available online and consider the following points:

- Discuss, with examples, the aims of behavioural pharmacology.
- What does the study of behaviour contribute to pharmacology?
- Discuss the contribution of the study of conditioned and unconditioned behaviour to behavioural pharmacology
- How can the effects of drugs on species-specific behaviours be objectively measured?
- Describe, with examples drawn from your reading, how drugs affect behaviour maintained by schedules of reinforcement.
- What has the use of drugs as discriminative stimuli told us about the biological basis of fear?
- How useful are 'simple' behavioural tests in the discovery of novel psychoactive drugs

- What are the limitations of animal models of psychiatric disorders? How may they be overcome?
- Describe the different types of animal model and make definition.
- Are the philosophical roots of behavioural pharmacology in ethology, evolutionary psychology, psychobiology or behaviourism?
- Describe an animal model which is theoretically based on psychological constructs.
- Describe an animal model which is theoretically based on pharmacological constructs.
- What is meant by the terms 'analogy' and 'homology' in physiological and behavioural characteristics? Why are these terms important to behavioural pharmacology?
- Explain, with examples drawn from your reading, the phrase 'reliable animal model'.
- "Mirror, mirror on the wall, who is the prettiest of them all?" Is 'predictive' the prettiest of all the validities?
- What are the most important properties of an animal model?
- To what extent is construct validity ephemeral?
- Does the learned model have etiological validity?
- What factors limit the development of models with etiological validity?
- Is etiological validity desirable (make validation definitions)?
- Will animal models based on genetic manipulations to produce animals with altered neurotransmitter receptor characteristics provide useful models of psychiatric conditions?
- Provide examples of the definition of a construct through convergent operationalism .
- Does 'face validity' provide any value to an animal model?

- Explain the term 'false positive' and 'false negative'.
- Explain the terms tolerance and sensitization.

ENERGY EFFECTS

So, summing up all stages of drug development we can say that introduction of a drug into the organism produces biochemical reaction which in its turn causes changes in potential energy of the body which conditioned by the internal energy of the body, entropy, thermodynamic energy and the energy of biochemical reaction. These energetic changes bring about energetic disbalance in animal body. After some time according to the law of energy preservation kinetic energy tends to change striving for balancing potential and kinetic energies. The energetic changes spread to the organism via cells causing behavioural changes. Drug effects are observed and studied through behavioural changes. We can make also the opposite assumption. Behavioural changes in animals are caused by biochemical changes in the body which in its turn brings to energetic changes in the body. E.g. we can say that when injecting the animal antidepressant, the organism relaxes and the animal in immobility state: it loses its vivacity and sensitivity. After some time the weight of the animal is growing, i.e. the potential energy of the animal decreases. This decrease goes with the decrease of kinetic energy (movability). The opposite assumption is: the animal loses its vivacity and it is getting into the state of immobility this process is combined with the decrease of total potential energy. Generally the total energy remains the same during relaxation time; the only change is which behaviour takes the major share of energy.

1. Understanding this one can say that all energetic changes and deviations come through all the stages of drug development and that is why energy or variables depending upon it are the most important statistical variable for the drug study.
2. It's necessary to make real-time measurements of energetic parameters in all stages of drug development.
3. It is needed to find statistical relationship between energetic changes and transfers of energetic change.
4. The intervals of abrupt energetic changes should be defined precisely and studied.
5. One needs to find the group of functional parameters which depends on energetic changes and to find out functional relationship between them.
6. The studies are conducted in matrix method (i.e. to choose the right group of variables during the studies and the group of functional relations between them based on the existing statistics).

The latter will help to draw more precise conclusions and will generate new ideas for solving the problems. This is very important for the struggle against cancer. Studying the energies of cell link it would be possible to turn it aside from the stage of development and make structural changes in cancer cells. Nanobiology and nanotechnologies are used in this type of research and keeping the new energetic balance by different methods and drugs as well as with new behaviours will encourage quick recovery from the disease.

Rule of energy preservation of the body.

The sum of the kinetic energy K and the function U (total potential energy) remains constant as the body moves around in the force-field. It should be clear, by now, that the function U represents some form of *potential energy*.

$$E = K + U = \text{constant} :$$

Where K is for the total kinetical energy and U is the total potential energy, particularly in case of absolute balance of kinetic and potential energies.

$$\mathbf{K + U = 0}$$

This formula is the equation of energetic balance.

Potential Energy of the Body

The potential energy of the body is dependent upon internal energy of the body, entropy, biochemical energy and thermodynamic energy.

Internal Energy

The total kinetic and potential energy associated with the motions and relative positions of the molecules of an object, excluding the kinetic or potential energy of the object as a whole. An increase in internal energy results in a rise in temperature or a change in phase. Strictly speaking, the internal energy cannot be precisely measured. This is because only changes in the internal energy can be measured, and the total internal energy of a given system is the difference between the internal energy of the system and the internal energy of the same system at absolute zero temperature. Since absolute zero cannot be attained, the total internal energy cannot be precisely measured. The same is true of other thermodynamic parameters such as entropy and the chemical potenial.

$$\Delta U = Q + W + W'$$

The First Law of Thermodynamics

The internal energy is essentially defined by the first law of thermodynamics which states that energy is conserved:

$$\Delta U = Q + W + W'$$

where

ΔU is the change in internal energy of a system during a process.

Q is heat *added to* a system (measured in joules in SI); that is, a positive value for *Q* represents heat flow *into* a system while a negative value denotes heat flow *out of* a system.
W is the mechanical work *done on* a system (W-is behavioural and measured in joules in SI)
W′ is energy added by all other processes

The first law may be equivalently in infinitesimal terms as:

$$\mathrm{d}U = \delta Q + \delta W + \delta W'$$

Although the internal energy is not exactly measurable, it may be expressed in terms of other similarly unmeasureable quantities. Using the above two equations to construct one possible expression for the internal energy gives:

$$\mathrm{d}U = T\mathrm{d}S - p\mathrm{d}V$$

chemical potential

In thermodynamics and chemistry, **chemical potential**, symbolized by ***μ***,

If we wish to express in a single equation the necessary and sufficient condition of thermodynamic equilibrium for a substance when surrounded by a medium of constant pressure *P* and temperature *T*, this equation may be written:

$$\delta(\varepsilon - T\eta + P\mathrm{v}) = 0$$

This equation represents total potential energy of the organism. Where **ε** is the internal energy, η is the entropy and **Pv** is the thermodynamic energy.

When δ refers to the variation produced by any variations in the state of the parts of the body, and (when different parts of the body are in different states) in the proportion in which the body is divided between the different states. The condition of stable equilibrium is that the value of the expression in the parenthesis shall be a minimum.

Kinetic Energy of the Body

Total kinetic energy of the body is often called energy of the mechanical work done by the body and it is assigned with symbol *K*.

$$\mathbf{K = mv^2/2 + m\omega^2R^2/2;\ \omega = 2piF}$$ **where F is the frequency**

In other words, the increase in the kinetic energy of the body, as it moves from point O to point X is equal to the decrease in the function U evaluated between these same two points. Another way of putting this is

$$\Delta U + \delta(\varepsilon - T\eta + Pv) = mv^2/2 + m\omega^2R^2/2$$

This is the equation of the energetic balance for the body.

$$\sum E_p = \sum E_k$$

$$\sum E_k = mv^2/2 + m\omega^2R^2/2$$

The latter is mechanical work, the energy of which can be obtained to a first approximation after processing the signal received from Laboras system. Differing from other detection methods of behaviours Laboras enables the researchers to make more accurate measurements of kinetic energy; one of its components depends upon motion (locomotion energy), the second component depends upon oscillation energy which is measured by other systems as infrared rays and using video systems to measure it is impossible because of the existing theoretic limitations.

E (locomotion energy) = $mv^2/2$
This is the kinetic energy depending upon the locomotion behaviour of the animal.

E (Oscilation energy) = $m\omega^2R^2/2$

ω - is for the frequency. This is the kinetic energy depending upon different movements of the animal without shift. Laboras system enables to measure these two types of kinetic energy while other automated systems for behaviour detection can measure kinetic energy being limited by one component, i.e. by locomotion energy.

Conclusion:

The theoretic limitations of the other systems for automated behaviour detection (video systems, system of infrared rays) are as follows:

1. Indirect contact with the animal, i.e. the animal has no direct contact with sensors (video camera, infrared sensors) located at a certain distance do not provide a possibility to measure oscillation energy as the oscillation radius (R) is too small compared with the distance from the sensors.
2. Dynamic focus of video camera (focus 1, focus 2, etc.) does not provide a possibility to measure precisely the ω oscillation frequency of such behaviours as Head Shakes, Scratching, and Wet Dog Shakes. The latter provides oscillation in conditions of immobility; they are of high frequency and have short duration.
3. The camera cannot embrace the animal completely (animal body is embraced only in certain segment of the camera).

One can say that currently Laboras is the only system which gives an opportunity to measure energy totally which enables to detect all types of complex behaviours even the very short ones starting from 0.1 seconds and above and the ones of high frequency (F = 15Hz and above).
So, we can conclude that all other systems can be used only for the detection of tracking parameters. These systems (video systems, infrared sensors) measure only

a part of the energy – Locomotion energy – but Laboras measures the total energy of animal behaviour as the system has direct contact with the animal through weight sensors. So, the researchers get quite pure signal through the Laboras system. After the processing of the signals it is possible to detect very complex behaviours of the animals such as Head Shakes, Head Twitches, Wet Dog Shakes, and Scratching which have short duration and high frequency. I.e. other automated systems for behaviour detection enable to detect only the behaviours which are connected with locomotion behaviour. Laboras system does not have such limitations as it is based on energy detection which is the most important parameter in all stages of drug development.

E–energy Dependent Parameters which Enable the System to Detect Behaviours

Behavior name	video system E(locomotion) $E = mv^2/2$	Infrared system E(locomotion) $E = mv^2/2$	Laboras system E(kinetical total)= E(locomotion)+ E(ostilation) E(Oscilation energy) = $m\omega^2R^2/2$
Locomotion	yes	yes	yes
Position + circling	yes	yes	yes
Velocity	yes	yes	yes
Climbing	yes	yes/no	yes
Grooming	yes/no 50%	no	yes
Eating	yes/no 50%	no	yes
Drinking	yes/no 50%	no	yes
Rearing	yes/no 50%	yes/no 50%	yes
Scratching	no	no	yes
Seizure	no	no	yes
WDS	no	no	yes
HS	no	no	yes
HT	no	no	yes
Formalin	no	no	yes

Laboras system for automated behaviour detection of Metris B.V. Company provides a possibility to detect accurately and record very weak, short and high frequency behaviours. Laboras system can also find and record very important statistics for the behaviour which are customer-specific: if the researcher gives the accurate definition of the behaviour and develops the list of necessary statistical parameters and functions then Laboras system has that option of determining that list and presenting it as it was required.

The group of parameters and functions provided by the researcher is very important: they have connections with all stages of drug development. And their accurate definition is necessary for the study process and the obtained results and it is extremely important to have the precise definitions and animal species which are input data for the solution of recognition problems.

The study will show excellent results if appropriate specialists for each stage of development are selected and the definitions for automated detection are accurately made.

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