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Toward Modeling the Human Physionome

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Abstract

The physionome is the description of the physiological dynamics of the normal intact organism. The march of science brings us now into the era where integration of the various facets of the knowledge of biology and medicine has become a major issue. Modeling is a vehicle for the combining of information from molecular biology, biophysics, and medical biology, but must be combined with strategies for databasing the raw data with greater efficiency than is currently possible. The lessons from the genome project can be applied to the next level major projects, the morphonome and the physionome, the objective being to put integrated forms of the data into the hands of physicians and medical scientists.

INTRODUCTION

The physionome is the description of the physiological dynamics of the normal intact organism. The root, “physio”, concerns nature. Physiology is defined as the study of nature, or the study of natural or normal function. The root, “nome”, means a part, as in binome, trinome, or means a name, as in nomenclature or classification. The “physionome” therefore means: a part of nature, and more particularly naming and describing of normal function.

Without stretching our imagination very far, one can nowadays classify biological science into a few broad categories that capture the essence of the fields of study. The inspiration for this comes with the success that followed the defining of the genome as a structure that contains the essence of life, the code that captures the phylogeny, and directs the ontogeny of animate organisms. Although regarded as a romantic notion when it was embarked upon two decades ago by a handful of scientists, it really represented a new paradigm for biological research: the large scale collaborative project designed to achieve a specific goal. Others whose titles mimic that of the genome will benefit from its strategies and from the realization that magnificent objectives are realizable.

Here are our “nomes”:

Genome: the sequence of bases in DNA and the locations of genes.

Morphonome: the structures of molecules, cells, tissues, organs, and organisms.

Physionome: the functions, kinetics, and regulation of the morphonome.

Psychonome: the state of mind, feelings of well being, fitness, and energy.

Socionome: the individual’s and the group’s relationships to others.

Long range strategies for the physionome need to be developed now. Given the magnitude of the set of knowledge that must be organized this won’t be at all simple; currently this type of project is simply ignored. It is enormously larger than any of the so-called grand challenges which have been forwarded to the scientific community over the past several years. The tendency to see it as impossibly large must be overcome, and the goals clarified so that the

"impossible" can be expressed as a set of perhaps very difficult but achievable goals. This is where there must inevitably be some hierarchical structuring.

Envisaging some of the pieces of the physionome is not a problem. Thinking of the heart, we could try to define the "cardionome", building a "theory of heart" (following the title of the text edited by Glass and Hunter [1]) that would provide a comprehensive picture of the behavior of the heart under a variety of physiological conditions. This would represent the integrated physiology of this organ, and even if not linked to the other parts of the body would still serve as a useful stepping stone. Other organs could be likewise used as "pieces of the physionome".

Structuring the physionome along organ system lines is inadequate from the point of view of the regulatory influences to which each organ is subjected, even though it might work in describing an isolated organ's *in vitro* or *in perfuso* state. Missing are the humoral, neural, psychological, and sociological linkages. By using the terms psychological and sociological in this context I mean to keep us aware of how the heart responds to complex internal feelings which are not mediated solely through neural influences directly on the heart, but through a complex mixture of neural, humoral, mechanical, and emotional influences. That these differ widely among individuals is well recognized. What are the causes of blushing in a psychopath compared to a normal sensitive person? Why do exercise, versus self neglect, induce such different levels of feeling of well being? How does being fit and healthy influence the normal responses to injury, healing repair, resistance to foreign substances and bacterial or viral invaders?

This kind of structure is like a huge pyramid, very broad, but not necessarily very high. At the lowest levels many of the pieces are the same for many tissues and organs; there are not very many different types of building blocks, but the same types of blocks are used at many sites. Even so, the number of blocks is large, and even a simple channel, a sodium channel, has different isoforms in different tissues, and may function a little differently in each setting. If there are 200,000 genes, each for a different protein, then the breadth of the pyramid is evident. But one can't start at the bottom and work upward rapidly for not all of the proteins and their reactions are yet known. In any case functional descriptions of organisms and organs did not and need not await knowledge of all of the details. So the question turns toward priorities and practicalities. Are there components of the physionome (Table 1) on which we have enough good data and which we can describe well enough to build realistic models of them, and can we structure such models in a modular fashion so that as our knowledge improves, the models can be corrected and augmented (Table 2)?

MODELS OF THE CARDIONOME

How simply could the modeling of a single organ be accomplished so that the result is both useful and reasonably accurate? What are the major features of myocardial structure and function that need to be brought together, and to what level of detail? Certainly many features can be omitted in the interests of obtaining a description of contraction and ejection of blood. A minimal model should contain a representation of the relationships between inflow pressures, ventricular pressures and outflow pressures. An example is the cyclical elastance model of the heart [2], a remarkably simple model adequate to give reasonable approximations to the pressure waveforms in the ventricle and aorta, and reasonable stroke volumes, and even reasonable durations of transients in response to changes in state.

There are many models or working concepts or data sets that serve as simple descriptors at this most primitive level. They are for the most part unrelated to each other: models for the spread of excitation over a layer of epicardium [3], models for purine metabolism and high energy phosphates [4,5], models for flow distribution throughout the heart [6], models for the action potential [7], models for fatty acid metabolism [8,9], models of excitation-contraction coupling

at the cellular level [10-12], models for calcium release from the SR [13], models for vasoregulation in the heart [14] and in skeletal muscle [15].

Models for various aspects of the cardionome can be expressed by using only parts of the extensive possibilities listed in Table 3. Models for an ionic channel, enzyme, or transporter would be at the molecular level and also require local feedback of information on concentrations of substrates, reaction products, and regulators at the subcellular level. Models for excitation-contraction coupling could be developed so that they are mainly at the cellular level, but would have to be modified by information available at the tissue level to account for influences such as the stretch dependency of channel conductances and ionic currents. Models for oxygen exchange and pH regulation would be at the tissue level with respect to solute exchanges, but at the cellular level for the binding, buffering, and chemical reaction. Models of cardiac mechanics would be mainly at the tissue and organ level. Models for coronary blood flow and its distribution require primary information at the organ level of intraorgan and intramural pressures, but with added information on perfusion pressures which are influenced by the state of vasoregulation throughout the body. Since one influences the other, body resistances influencing the pressures available for coronary perfusion and coronary perfusion influencing force generation and cardiac output such models should be considered in the same fashion as transcendental equations, namely that they are solved by allowing them to run to steady state. (They will not run to equilibrium, a state which exists only after death. In fact almost no intracellular reaction is at equilibrium, but many run at near-equilibrium states with net fluxes that are much less than unidirectional fluxes.)

Modeling is clearly a part of the integrating character of the physionome project. In theory, the ultimate model of the cardionome would be one in which the blood flowing through the cavities and the tissues of the heart could be defined in terms of its composition and its pressures at the various inflow points, including the concentrations of regulatory hormones, and the autonomic outflow, and the fully detailed model would give the appropriate response. The current state of the art is that the cardionome's subsidiary models have only a relatively few variables, and can usefully represent very circumscribed states. Nevertheless, given that a useful long range goal is the full "cardionome" model, these limited models provide steps in the right direction.

The problems are that now we have neither good databases, nor good standard models, both of which should be publicly available. By that I imply that it will not be even possible to develop comprehensive models until very extensive databases are available in well organized fashion so that their information can be used when integrated via the model. What will inevitably occur when such archived data are used in comprehensive models is that either the model will be proven wrong (as they all are, in the sense of being either incomplete or incorrect), or some parts of the database will be found to be contradictory to others (which is bound to occur when not all the data have been obtained simultaneously from a single animal). The best model cannot be a perfect representation of any particular model, but is merely a representation of an average state of an average organism of a particular species.

This raises the question of what should be the prime target species, the focus of the data gathering and modeling: a particular animal species or a human? If the dog, should a particular breed be chosen for parsimony in building the database? Can the database be constructed in a fashion that is not race-blind or species-blind, for the distinctions are important in understanding the functional physiological behavior of the individual, but so as to accommodate the wide variety of species and subspecies on which data are naturally gathered in our laboratories? If there is to be a focus on human data, are we in a position to gather it in this day and age of serious political and social encumbrances to data acquisition? Is it possible to find any species on which all types of data can be gathered or must we continue to make, and be misled by, the inference that one species is much like another?

STRATEGIES FOR THE PHYSIONOME PROJECT

The overall strategies involve the science and the politics of supporting and integrating the science. The social compact, the covenant between scientific workers and their supporting agencies representing the people and the state, by which scholarly effort offers benefits to society so that the society will invest in the effort, is currently being challenged by those who feel that research is no longer needed. Such views will have to be overcome. At this point it is evident that even the funding agencies have difficulty in being a force for integration, and this is left to the scholarly community and to the writers of science fiction.

Nevertheless, beginnings can be made, for much has been learned from the Genome Project [16] and more will be learned before it is complete. We can begin with the simpler and more obvious and more practical aspects of the physionome project, perhaps as follows.

1. Promote Extensions of the Scientific Method

A hypothesis cannot be proven, only disproven, and disproof is usually quantitative rather than qualitative. Make the hypothesis quantitative. Give equations, and formulate the model. Use it in experiment design. Define the most critical test of the idea. Devise an alternative hypothesis, and treat it likewise. From this, devise the single experiment or the set of experiments which clearly test the distinction between the two hypotheses. (The result is new knowledge, a real advance and not merely acceptance of the status quo: One hypothesis must die! Maybe both!) At the same time, at a less formal level, encourage the recording of the unexpected observation that does not fit in with previous notions, for these may be the most precious ones of all.

2. Build Hierarchical Sets of Models

This is a variant of what has been termed the reductionist approach. Start with the lowest level blocks, e.g., the detailed kinetic behavior of a purine transporter or a channel. Include the influences of competitors, blockers, pH, potential, etc. At the next hierarchical level, e.g., in an excitation-contraction coupling model, use a reduced version of the channel model, one which provides the correct fluxes under the given circumstances, as a limited but efficient representation. Instead of using the general flexible channel model, use one of a set of distinct reduced models. Repeat this strategy at the next level, e.g., in building models for force-velocity relationships at different heart rates.

3. Target Subsets, and Organize a Cooperative

Gather experts, and meet to define targets and assign tasks. Develop multimedia network connections for conferencing in reviewing data and models by staff of several institutions simultaneously via Internet. Develop database configurations and standards. Write model code under a “source code control system” so that it is testable and reviewable by staff at several institutions. Code for clarity and portability in accord with code standards and modeling standards. Obtain funding for focussed central resources to archive and maintain model code and its support packages, parameter databases, exemplary experimental data, targeted facets of morphonome and genome data for each target area. (These should be narrowly enough focussed that resource personnel are expert in the particular areas of study.)

4. Organize the Task Force

Establish resource facilities for special fields. Each one could serve as a large integrating center for a target such as hypertension, diabetes, atherogenesis, etc., that is, have clinical disease focus. Others could have a focus on an organ system: heart, lung, liver, brain, bones, etc. Still others would be centers for tissue studies: autonomic nerves, interstitium. Resources for

cellular functions (RBC, neutrophils, myocytes, etc.) would still be comprised of fairly large groups. Yet others might be biophysical or biochemical resources concentrating on transporters, channels, pumps, enzymes, molecular dynamics, and biochemical subsystems. These latter would necessarily build upon the genome and morphonome. Within each resource one would attempt to devise small model systems that can be linked to those of other resources. By having such foci of expertise and open lines of communication one may hope to integrate (models and scientists) early in the development of the physionome, and thereby obtain some understanding of how both the physionome and the scientific system works.

5. Develop an International Infrastructure

Develop support of research at an integrative level. Organize symposia at each society's national meetings. Define and develop the required technologies: a database such as Physbank with linkages to Genebank, on-line reference libraries to detailed information (Enzyme Handbook), and establish at each center directories available via ftp for model code with test routines. Organize workshops, Gordon conferences, and symposia on particular topics. Establish training programs at pre-and postdoctoral levels. Establish consultation services at each center.

SUMMARY

The physionome is proposed as an integrating concept describing the function of an organism. The concept serves as a vehicle for defining a "Physionome Project" around which one can establish lines for collecting, reviewing and retrieving data, and using the data to formulate an understanding of physiological function in an intact organism where multiple interactions between systems is the norm. The Physionome Project would be a huge enterprise, and so can only be undertaken via a long scries of steps, with scientists of many labs and many nations working in concert to test each others' ideas and approaches. At each stage of the development there would be rewards in the form of improved understanding of how the body works and of how it can malfunction.

DISCUSSION

Dr. E. Ritman

I am left with a feeling of "what do I do now?" You have presented too much. But there is an area where you might elaborate a little bit even though you've given us too much already to think about. In the physionome, if you took a liver and ground it up so that the cells stay intact, that bucket of cells would behave very much like the liver in many respects. You could do molecular and genetic medicine and biology and come up with answers as we do now for organs that we grind up.

Dr. J.B. Bassingthwaighte

You do not really believe that!

Dr. E. Ritman

That is the point I'm getting to! The one thing you might emphasize is the basic functional unit. There is the hepatic lobule, for instance, or the nephron in the kidney, or the haversian canal system in the bone, or the terminal bronchiole with its alveoli. These are sort of morphological units, certainly basic functional units that have the function that is multiplied to give the total organ function. But if you had even one basic functional unit, it will behave like the organ and just looking at the major cell components of that basic functional unit, you will not duplicate the organ function. This is something that we should pay more attention to. I am not sure what the basic functional unit of the heart is, for instance, but one beginning is

to identify one arteriole with its capillaries and the associated muscle cells that are perfused by that. It may be something different, but once you have that, then you have a structure that the people from the molecular domain can aim at and other people can aim at in terms of the given functional unit, i.e., how does that impact on the macroscopic structure and function of the organ.

Dr. J.B. Bassingthwaighte

That is a good point. If we took a small piece of the heart and determined its biochemical and ionic regulatory functions and how they related to sarcomere shortening, we would then face the next problem on how to arrange that set of units so they would be connected appropriately to each other. One has the hypothesis, for example, that there is a sort of an impedance matching relationship between flow, transport capacity of membranes and enzymes, metabolic energy utilization, and work locally. Then one would have to arrange those units so that the work units have the correlation structure that allows the ventricle to contract appropriately and for this, one has to have an appropriate representation of velocities of propagation and the direction along the excitation pathways. There are these multiple levels of integration that are occurring through the set of tissues. The liver certainly needs its arrangement along the sinusoid. The enzymes are different at the upstream end of the sinusoid from the downstream end of the sinusoid. Some enzymes only exist at just a few terminal cells along the sinusoid toward the hepatic vein. There is this heterogeneity within a functional unit, usually axially related to inflow and outflow in a metabolic organ like the liver, and in other ways in the heart. So it is rather complicated. Where should we start? Maybe we have already started. We are each looking at pieces and putting them together in broader and broader ways. Some of the following chapters will present ways of putting the whole organ together.

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Table 1

Hierarchical Structure of the Physionome

1	The overall physiologic state of the organism: healthy or impaired, resting or stressed, conditioned, aged, overall functional adequacy.
2	Organ level function: Blood flow, oxygen consumption, utilization of substrates and production of metabolites, hormones, etc., energy balance, adequacy to maintain normal function over a range of conditions of the organism. For the heart this level would include stroke output, heart rate, pressure output, work, energy consumption, substrate consumption. flows. Relation to organism: neural humoral, mechanical feedback.
3	Intraorgan regional variations: Differences in functions such as regional flows, substrate uptake, metabolism, work (internal, external) For the heart: atria versus ventricles, contractility, heart rhythm and rate, contractile tension, myocardial deformation and relaxation, propagation of excitation
4	Tissue and cells: cellular physiologic and biochemical functions, mechanical and physicochemical features, composition and anatomic measures, blood-tissue exchange, metabolic fluxes, intercellular communication, traffic along biochemical pathways, all of which contribute to stabilizing the volumes and the concentrations in cells and in intercellular spaces.
5	Subcellular constituent and protein level, the basic biophysical, biochemical levels of subcellular function: Pumps, channels, enzymes, receptors: activation, inhibition, rates, competition, regulation.
6	Molecular behavioral level: Protein conformational states: site accessibility, channeling, sensitivity to pH, etc., molecular abnormalities.

Table 2

Reasons for Undertaking the Physionome Project

1	Databasing and modeling produce integrated knowledge for practical understanding.
2	Groups of related hypotheses, based up until now on small separate sets of observations, can be put together and tested for contradictions. This results in increasingly strong and more general hypotheses which have been cleared of internal contradictions, and which represent larger and more comprehensive sets of data.
3	The existence of “accepted”, standard, comprehensive models aids refuting incomplete and incorrect hypotheses. It also enlarges the risk that investigators will be attracted to build only on the “party-line” model, so attention should be paid to the development of competing models of large systems, with the natural and explicit goal of determining which one, if either, is correct. This aids in experiment design: experiments should be designed to distinguish between alternative hypotheses, so that one is doomed to learn something from the results which should prove at least one of the models wrong.
4	Increased efficiency in experiment design helps to minimize the numbers of animals studied.
5	Teaching and training can make use of integrated model systems in both basic sciences and in medical practice situations. Such usage illustrates that quantitative approaches to biology are worthwhile.
6	The physionome and its many components would provide not only comprehensive databases which are not currently existent, but also integrated, analytical approaches to the study of medicine and physiology.
7	The establishment of a defined broad umbrella for many focussed yet integrated targets generates foci of interdisciplinary collaborative activity, and provides a means of bringing the efforts of many laboratories into a single self-consistent framework.

Table 3

The Cardionome: A One-organ Component of the Physionome

Molecules	*Structure:*	of proteins for channels, pumps, receptors, enzymes, junctions, contractile apparatus, binding sites.
	State:	conformational state, receptor occupancy.
	Kinetics:	activation energies for changes of state, diffusion, reaction, aggregation.
	Function:	transport, catalysis, signalling, energy transduction, regulation.
Organelle	*Structure:*	mitochondria, SR, Golgi, nucleus, gap junctions, T-system.
	State:	electrochemical potential, pH, pCa.
	Kinetics:	substrate and 0_2 usage, ATP production.
	Functions:	sequestration reactions, microenvironment creation.
Cell	*Structure:*	cell, shape, size, arrangements of organelles.
	State:	membrane potassium, energy stores.
	Kinetics:	cellular function, rate of output of product.
	Functions:	ionic balance, action potential generation, calcium regulation, tension development, response to stretch.
Tissue	*Structure:*	cell arrangements, interstitial matrix, capillarity, fiber direction and cross connectivity, mechanical linkages (collagen to cytoskeleton), vascular arrangement.
	State:	material composition, mechanical properties.
	Kinetics:	blood-tissue exchange, deformation, excitatory spread.
	Functions:	solute exchanges between cells, blood-tissue exchanges, propagation of excitation, generating shortening stresses and strains.
Organ	*Structure:*	fiber arrangements, anisotropy, directed spread-of-excitation.
	State:	contraction, relaxation, inflow, outflow, innervation.
	Kinetics:	rate of deformation, ejection velocity, cardiac output, pressures (Coupling with body, e.g., output impedance).
	Function:	coordinated spread of excitation, cardiac contraction, volume ejection, responses to humoral agents and autonomic outflow, ANF production.