Overview

By *Jochen Mau*[1] *(ed)*

Abstract: The book presents BIOKYBERNETIKA in its original definition as "multiscale biomathematics for coherent modeling of human-body system" under four aspects, (I) axioms and theory assumed to lead to applications, (II) applied models prior to or including their empirical investigation, (III) technologies and methodologies that expand range and depth of applications, and (IV) mathematics in support of research and practice in clinical medicine.

Part I: Theories

Part I-A: Overarching theory

1. Universal axioms in classical Chinese philosophy

Chapter by Yi Feng and Jochen Mau [pp. 5–14]

Method Axiomatic biodynamics of a whole human-body system are based on a hierarchy of units that solve their assigned functional tasks by ubiquitous energizing charge in supply and demand, (cf. 3).
Application Key concepts of neo-Confucian classic *Book of Changes* hold that all things in Universe have nature *ti*, function *yong*, with structure *li* and energizing charge *qi* as respective aspects. For driving force of *qi* dynamics, the older classic of *yin* and *yang* is invoked.
Outcome Their interpretation as "demand" and "supply" of energizing charge completes the match of concepts; for formal proof of isomorphy, objects and relations have to be cast into mathematical categories (cf. 2).

2. Category theory for structural characterization

Chapter by Jochen Mau [pp. 15–43]

Method In complex dynamic systems, category theory is used for a mandated prior analysis of the system's structures of effectuation ("wirkgefuege") in which functional dynamics evolve.

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Application By the Yoneda embedding, any object's relations with all other objects in the same category characterize that object completely and uniquely—implying a mathematically rigorous "noninvasive," hence "nondestructive," exploration of not fully understood real-world objects.
Outcome Applications arise in modeling surrogates by analogy, behavioral profiling, and implementations of artificial intelligence (AI).

3. Axiomatic bipolar dynamics and their control

Chapter by Jochen Mau [pp. 45–73]

Method By the cobweb theorem of economics, demand and supply are brought to match in market equilibrium and effects of small disturbances in its vicinity depend on their relative elasticities, meaning return to equilibrium, oscillation, or spinning-off.
Application The concept is applied to functional dynamics in hierarchical structures, that express in transfer of energizing charge for transformation into task-solving functional energy upon a supply–demand match, at every level.
Outcome The mechanisms of control in economic theory are applicable and upscalable for a coherent holistic systemwide control.

Part I-B: Systems theories

4. Stochastic formalization of agent-oriented systems

Chapter by Sergey V. Bogomolov, Vyacheslav A. Sapozhnikov, and Roman Yu. Yurmalnik [pp. 79–107]

Method Multiscale systems are represented holistically by a hierarchy of mathematical models that span from microscopic to macroscopic levels.
Application The theory can be applied to study very large systems of complexly interwoven stochastic dynamic structures in correct mathematical forms.
Outcome This permits faster and less costly assessment of interventions *in silico*, when compared to real-life evaluations of effects of policy changes, e. g., in epidemic response.

5. Simplification of high-dimensional multitempo dynamic models

Chapter by Lijun Zhang, Elena Shchepakina, and Vladimir Sobolev [pp. 109–122]

Method When a dynamic system is linear in fast variables, an exponentially decreasing part may be decoupled from an independent part of solutions. The first usually describes the main process, the second transient ones.
Application Practicality is demonstrated in chemical kinetics for the glutamate transporters model and bacteriophages interaction models, where the first system usually describes the main processes and the second transient processes.
Outcome A significant simplification of differential systems can be achieved in some classes of dynamic models for which it is possible to reduce dimension and eliminate computational rigidity.

6. Ideas of symmetry as a biophysical basis of system biomedicine

Chapter by Vsevolod Tverdislov, Alla Sidorova, Olga Bagrova, Ekaterina Belova, Aleksey Lutsenko, Ekaterina Semenova, Denis Shpigun, and Natalia Levashova [pp. 123–147]

Method Chiralty of helical, superhelical and irregular structures of proteins are assessed and formation of protein structure from an irregular and a regular part is modeled.
Application Implications for drug development are shown in the classification of 100 chiral drugs in regard of induced side effects or lower therapeutic effects.
Outcome The concept of chirality of biomacromolecules can contribute significantly to theoretical molecular biology and mathematical modeling that focuses on folding and docking processes. The hypothesis of the existence of a sign-alternating chiral invariant was substantiated and a relationship between the chiral solubility of drugs and its effect on a specific molecular target was established.

7. Disorder of multiscale control

Chapter by Shuchang Wang and Guanyu Wang [pp. 149–184]

Method Multiscale dynamic analyses including singularity and bifurcation analysis of cellular insulin signaling network, optimization based mathematical analysis of plasma glucose-insulin homeostasis, agent-based computational modeling to integrate complexities at multiple biological levels from cell to organism.
Application We studied the molecular dynamics of a cell in response to insulin, the necessary condition for optimal glucose homeostasis, the physiological role of insulin resistance, and insulin mediated peripheral network of nutrients utilization.

Outcome The link between metabolic syndrome and cancer lies in the shift in three patterns of cellular insulin response, in which the normal hysteretic bistable control is necessary for optimal glucose homeostasis. The insulin response threshold has provided a mechanistic basis for insulin resistance, which plays an indispensable role in regulating both glucose and fat homeostasis.

Part II: Person's life-sphere

Part II-A: Person's biosphere

Part II-A.1: Body's cellular system

8. Mutations as activators of biological evolutionary processes at population levels

Chapter by Alla Sidorova, Natalia Levashova, Anastasya Garaeva, Vsevolod Tverdislov, and Raul Argun [pp. 189–208]

Method Accumulation of small fluctuations as quantitative changes in a nonlinear dynamic system's parameters can induce a transient instability before a new stable state is reached—a standard concept in self-organization.
Application It can be traced in three areas: In biological evolution, when genome and coding parts dynamic are modeled. In populations, when new mutations enter a heterogeneous population with previously established mutations. In laboratory mice, in number of negative mutations for occurrence of phenotypic differences.
Outcome The models considered can be applied in the field of genetic engineering and in the analysis of the conditions for spreading negative mutations during epidemics.

9. Immunometabolism of T-cells in COVID-19

Chapter by Jian Li, Junping Yin, Christian Kurts, Xiangpan Li, and Qi Mei [pp. 209–243]

Method A robust and quantifiable immunometabolic profile derived from the modeling of single-cell data of T-cells with metabolic flux analysis is summarized in the metabolic activity scoring system.
Application This scoring system was applied to differentiate the metabolic states of T-cells under different disease conditions, including acute and convalescent COVID-19 infection of differing severity.
Outcome Utilization of this immunometabolic scoring system might lead to a better basic science understanding of pathogenesis and host response in COVID-19 infection and could be developed to a clinical tool to monitor therapeutic efficacy and to predict outcome.

Part II-A.2: Body's vital functions

10. Structural modeling of vascular networks

Chapter by Veronika S. Kopylova, Stanislav E. Boronovskiy, and Yaroslav R. Nartsissov [pp. 249–281]

Method Modern approaches to vascular network modeling that are highly diverse and include complex computer models for wide range of biophysical processes and spatial scales are reviewed.
Application These methods have greatly expanded the possibilities of studying vascular systems and application of these models in medicine, opening up new prospects for the diagnostics and treatment of diseases.
Outcome At the moment, the problem of taking into account specific tasks in order to ensure a balance between accuracy, factors under study, and computational costs comes to the forefront.

11. Mathematical modeling of AI application for the diagnosis of blood flow disorders

Chapter by Egor V. Kochetov, Anna Ya. Bunicheva, and Sergey I. Mukhin [pp. 283–302]

Method For a set of circulatory pathologies, virtual databases for learning and diagnostics are formed by using mathematical models of blood flow by approximation of quasi-one-dimensional hemodynamics.
Application The procedure is applied to diagnosing blood flow pathologies based on the patient's pulse wave data and permits prior computer modelling of AI methods now in use for that purpose. Feasibility and practicality are demonstrated.
Outcome As implementation and verification of AI methods require significant time, involve high material costs, and successful results are still not guaranteed, the approach is suitable for prior evaluation of the accuracy to be expected from AI in this context.

12. Modeling of glucose and insulin regulation within the framework of a self-consistent model of the cardiovascular system

Chapter by Alexander Khrulenko, Kseniia Mysova, and Anatoly Pokladyuk [pp. 303–318]

Method Algorithms for convection-diffusion transport in closed circulation are developed for the Cardiovascular Simulating System (CVSS) software that is based on hemodynamics in a quasi-one-dimensional structure.

Application Storage and release of glucose in the liver and interdependent regulation of insulin secretion from the pancreas are simulated under various conditions.
Outcome Modeling the processes underlying glycemia formation within closed circulatory models facilitates the acquisition of physiologically consistent results. Therefore, it offers opportunities to test and advance diagnostic and therapeutic technologies for glucose metabolism disorders.

13. Hemodynamics in residual myocardial ischemia

Chapter by Sergey Simakov, Timur Gamilov, Alexander Danilov, Philipp Kopylov, Peter Chomakhidze, and Fuyou Liang [pp. 319–333]

Method Hemodynamic indices of myocardial perfusion are evaluated by numerical simulations within a 1D network dynamic model of blood flow, personalized by construction of coronary hemodynamics from computed tomography (CT) images.
Application After Percutaneous Coronary Intervention (PCI), using only the standard parameters—fractional flow reserve (FFR), coronary flow reserve (CFR), and instantaneous wave-free ratio (iFR)—may suggest false-negative recovery of coronary circulation, meaning not to detect a residual myocardial ischemia.
Outcome By simulations, fractional flow reserve (FFR) is estimated with the same accuracy as instrumental invasive measurements and errors are comparable to the uncertainties of input patient-specific data. High fractional flow reserve (FFR) and high instantaneous wave-free ratio (iFR) values do not necessarily correlate with improvement in coronary flow reserve (CFR) or with long-term recovery of coronary blood flow.

14. The quasi-one-dimensional model of the lymph flow in the human lymphatic system

Chapter by Anastasiia Mozokhina and Sergey Mukhin [pp. 335–363]

Method The transport function of the lymphatic system is developed from the quasi-one-dimensional approach established for cardiovascular circulation.
Application It is modified for unidirectional lymph flow in elastic tubes with valves. The model is general enough to permit investigation of several mechanical factors on lymph flow, in presence and absence of gravitational force.
Outcome Self-contractions of lymphangions together with the valves, the so-called lymphatic muscle pump (LMP) is a major driving force of lymph flow. In the presence of natural gravitational force, sufficient elasticity of lymphatic vessels is essential.

15. An integrate-and-fire mechanism for modeling rhythmicity in the neuroendocrine system

Chapter by Alexander N. Churilov and John G. Milton [pp. 365–376]

Method A new impulsive mathematical model of a hormonal axis is developed and then investigated using computer simulations.
Application It is applied to hormonal rhythmicities observed in health, in disease, and in response to treatment.
Outcome The model exhibits a variety of complex rhythmic behaviors (circadian and ultradian), which are close to those observed. It hence provides some mathematical explanation of complexity in hormone variation.

16. Kinetic network modeling of the neuroendocrine hypothalamic-pituitary-adrenal axis dynamics with particular attention on the role of alcohol as a digestif

Chapter by Ljiljana Kolar-Anić, Željko Čupić, Ana Stanojević, Stevan Maćešić, Milorad Anđelković, and Vladana Vukojević [pp. 377–392]

Method By a kinetic network modeling approach in the form of stoichiometric relations that describe interactions between basic constituents of a system, biochemical transformations occurring at lower levels of organization are integrated and can evoke specific dynamical behavior at a higher level of organization.
Application Applied to relations between essential hypothalamic-pituitary-adrenal (HPA) axis hormones, HPA axis dynamics can be emulated quantitatively under basal and perturbed (stress) conditions.
Outcome Results are consistent with common experience that the order in taking food and alcohol is relevant for moderating ethanol effects. Particularly, taking cholesterol-rich food before alcohol consumption may partially decrease (mitigate) the effects of alcohol on HPA axis activity.

17. Inflammation and immune response in atherosclerosis

Chapter by Ghada Abi Younes, Wissam El Hajj, Nader El Khatib, and Vitaly Volpert [pp. 393–421]

Method A qualitative understanding of the complex biological and biochemical processes of development of atherosclerosis is depicted through mathematical models.

Application Mathematical modeling of this multifaced disease provides insights into the mechanisms driving lipid accumulation, inflammatory response, plaque formation, and rupture.
Outcome Through ongoing enhancement of these models and their integration with experimental and clinical research, we can develop more effective strategies for preventing, diagnosing, and treating atherosclerosis.

Part II-A.3: Body's motor functions

18. A magnetic resonance spectroscopy approach to quantitatively measure GABA and phosphorus level changes in the primary motor cortex elicited by transcranial direct current stimulation

Chapter by Chang-Hoon Choi, Harshal Jayeshkumar Patel, N. Jon Shah, and Ferdinand Binkofski [pp. 427–439]

Method Integration of transcranial direct current stimulation and magnetic resonance spectroscopy offers a robust, noninvasive methodology for investigating the intricate relationship between neuronal plasticity and energy metabolism.
Application By concurrently modulating and measuring neuronal excitability, energy consumption and metabolite concentrations, this technique enables us to gain profound insights into the biochemical and physiological processes underlying both healthy and pathological brain states.
Outcome This combined approach holds significant promise for advancing our understanding of brain function and for the development of novel therapeutic interventions for neuropsychiatric disorders. Consequently, this could lead to the development of more effective treatments and better mental health outcomes.

Part II-A.4: Body's operational functions

19. The fermionic mind hypothesis – a category-theoretic verification of consciousness

Chapter by Eva Déli [pp. 445–457]

Method Structural organization of physical matter and intellect is compared by recourse to mathematical category theory where objects can be characterized completely through all relations they have with others objects, a result known as Yoneda's lemma.

Application Applying this to the smallest known components of matter and of intellect, fermions and consciousness, organization of the brain and of physical matter appear categorically equivalent.
Outcome This characterizes consciousness as a temporal fermion according to the fermionic mind hypothesis (FMH), and holds the potential to enhance understanding of mental conditions, guide medical and technological advancements, and provide a physical basis of intellect that may set standards in developing artificial consciousness.

20. Cross-task cognitive workload measurement based on the sample selection of the EEG data

Qi Wang, Xin Xie, Jianhua Zhang, and Zhong Yin [pp. 459–473]

Method An EEG sample selection method, integrated with four classical machine learning classifiers (multilayer perceptron, K-nearest neighbor, logistic regression, and support vector machine), was developed for cross-task cognitive workload recognition.
Application The classification system was applied to two EEG databases to validate its generalizability in distinguishing binary workload levels.
Outcome This method can be used to develop workload assessments that are adaptable to operator specific features in human machine systems.

Part II-B: Person's eco-sphere exposures

Part II-B.1: Living nature cohabitation

21. The spread of SARS-CoV-2 in Russia and the evolution of the properties of the pathogen

Chapter by Andrey Gerasimov [pp. 479–489]

Method The classic Susceptible—Infected—Recovered (SIR) model of epidemic dynamics is extended for inclusion of antiepidemic measures, seasonal factors, and pathogen mutations.
Application Applied to the SARS-CoV-2 family with its highly variant mutations during the COVID-19 pandemic, academician Belyakov's theory of self-regulating parasitic systems is mathematically confirmed.
Outcome That conveys the hope that evolution of disease severity during mutations of the pathogens will decrease and infections become a "normal seasonal disease."

22. Agent-based modeling of epidemic spread via kinetic Monte Carlo method

Chapter by Rui Tang, Alexei G. Makeev, and Natalia L. Semendyaeva [pp. 491–512]

Method A stochastic agent-based model of epidemic spread has been developed, utilizing an effective kinetic Monte Carlo algorithm for modeling of population dynamics.
Application It is used to study the conditions for emergence of a protracted pandemic, accompanied by formation of a state of spiral chaos in the system.
Outcome This approach to mathematical modeling of epidemic spread makes it possible to assess the role of quarantine measures and necessary vaccinations to stop the circulation of the virus, and hence presents an effective tool for planning antiepidemic measures.

23. Control of outbreaks in China's provinces 2020

Chapter by Jochen Mau and Wenhua Tian [pp. 513–530]

Method An occurrence-exposure (O/E) ratio relates total number of cases to total time on test (TTT) for estimation of a constant hazard. The Bateman function from pharmacokinetics and its power series approximation to power ten both represent fast absorption but differ in slow and fast elimination, respectively.
Application Evolving outbreaks of SARS-nCoV wild-type in China, early 2020, are compared retrolectively for constant attack rate and changes in speed of spread between several provinces. Power-10 series approximations are fitted to the sugar-loaf shapes of log-incidences that are characteristic for quickly suppressed outbreaks.
Outcome By taking an epidemic outbreak as outburst from a hidden "pool" of infected like discharge from a capacitator, classical mechanistic models are not involved and guesses about *a priori* unknown parameters not required.

Part II-B.2: Civilization

24. Pesticide exposure: Toward holistic environmental modeling

Chapter by Nadezda A. Vasilyeva and Artem Vladimirov [pp. 535–557]

Method A hierarchical coupling strategy can be used, starting with the integration of models exhibiting the greatest similarity. However, this approach can be computationally expensive due to the need for data exchange between models.
Application Coupling models with diverse structures across multiple scales in holistic modeling of substance fate in ecosystems.

Outcome Utilizing efficient and universal data structures like octree/quadtree forests can significantly reduce the need for data transformation in transfer between coupled models.

Part II-C: Person's socio-sphere exposures

Part II-C.1: Economic factors

25.Evolution of the health system in Shanghai, China, 2016–2020

Chapter by Wenhua Tian [pp. 563–575]

Method For quality assessment of health care systems, the Donabedian model uses sets of indicators for structures, procedures, and outcomes.
Application The comprehensive health system of Shanghai, a 25-million megacity, financial and economic center on East China's coast, was evaluated by its 2016–2020 data.
Outcome Shanghai's health system has reached the levels of performance that global economies have, with less input of health resources and a higher output in health indicators, meaning that it uses its resources more efficiently.

Part III: Technologies

Part III-A: Engineering sciences

26. Design-process automation using functional process blocks

Chapter by Samuel Vogel [pp. 581–599]

Method Design-process automation by functional process blocks (FPB) can avoid some of the drawbacks of currently used approaches.
Application Notwithstanding investigation of its merits in practice, there is no difference on a formal level between engineering and mathematical or control models in biology and medicine.
Outcome The proposed method of design-process automation then holds promise to equally automate processes of identification and optimization for models presented in this book, BIOKYBERNETIKA.

27. Slow/fast dynamic models with applications to engineering problems

Chapter by Sergei Sazhin, Elena Shchepakina, and Vladimir Sobolev [pp. 601–611]

Method Geometric theory of singular perturbations combined with asymptotic technique is used.
Application Modeling of critical phenomena during gas combustion, including slow combustion and thermal explosion.
Outcome To separate different combustion regimes, the value of the heat loss parameter corresponding to the critical regime is identified.

Part III-B: Information sciences

28. Numerical modeling of medical ultrasound using the grid-characteristic method

Chapter by Katerina A. Beklemysheva, Igor B. Petrov, Evgeny V. Pyriaev, and Alexey V. Vasyukov [pp. 617–633]

Method A grid-characteristic numerical method on tetrahedral grids allows to solve the three-dimensional system of equations for a viscoelastic material even in a complex shaped computational domain.
Application It was applied to ultrasound examination in heterogeneous media and allowed to obtain the wave patterns including not only longitudinal waves but also shear waves and surface waves that appear in bones or implants but are not taken into account by solutions based on acoustic approximation.
Outcome This approach is computationally expensive, but it allows to explain certain artifacts and may be used to predict new ones and filter the ultrasound image to improve the quality of diagnostics.

29. The direct and the inverse magnetic encephalography problem

Chapter by Ivan P. Pakhnenko, Arthur I. Sabirov, and Tatyana V. Zakharova [pp. 635–650]

Method A combination of the signal decomposition method with other localization methods can achieve acceptable accuracy in the inverse problem of magnetoencephalogy. Combination of basin hopping with the limited memory Broyden–Fletcher–Goldfarb–Shanno algorithm (L-BFGS) can improve the quality of approximation.

Application Enhanced magnetoencephalography (MEG) is used when damaged tissue must be localized with high accuracy, prior to neurosurgical operations.
Outcome Though presented for two dipoles, much more complex problems can be treated without loss of quality and speed. We are currently working on an expanded applicability of the method.

Part III-C: Data-analytic sciences

30. Assessing the bioequivalence of two different drugs with the same active ingredient

Chapter by Margarita A. Dranitsyna, Victor K. Klimenko, Pavel V. Panov, and Tatyana V. Zakharova [pp. 655–664]

Method Bioavailability of a pharmaceutical is quantified as area-under-the-curve (AUC) of concentrations determined at prespecified times after application. For comparative biovailability experiments, a statistical test was developed to control the statistical type-I error in presence of missing concentrations.
Application Testing for equivalent bioavailability of two pharmaceutical preparations of the same active ingredient of a drug is important in regulatory decision-making about prescribability of the new preparation in market however missing blood samples can give rise to uncontrolled chance occurrence of a type-I error, known as α inflation.
Outcome The proposed criterion keeps the predetermined α level and is more sensitive to differences in average bioavailability than the two one-sided tests (TOST) procedure.

31. Estimation of adjusted relative risks in log-binomial regression using the Bekhit–Schöpe–Wagenpfeil algorithm

Chapter by Stefan Wagenpfeil, Jakob Schöpe, and Adam Bekhit [pp. 665–676]

Method A maximum likelihood estimation (MLE) procedure with linear constraints tailored to log-binomial regression is developed and implemented in the Bekhit–Schöpe–Wagenpfeil (BSW) algorithm.
Application A wide range of previously met problems with nonconvergence in ML-estimation in log-binomial regression can be avoided without any artificial work-around.
Outcome The algorithm is stable, locally quadratic, and globally convergent, hence recommended for estimation of adjusted relative risks in the general context of prospective epidemiological studies.

Part IV: Clinical medicine

32. Finding optimal two-stage combined treatment protocols for a blood cancer model

Chapter by Evgenii N. Khailov, Nikolay L. Grigorenko, and Ellina V. Grigorieva [pp. 681–695]

Method To find an optimal time at which to switch treatment regimes, a two-dimensional Lotka–Volterra competition model with two bounded control functions is used.
Application An initial treatment regime aims to stop proliferation of tumor cells for a partial or complete remission in which a second regime maintains suppression; concentrations of healthy and cancerous cells are the variables.
Outcome The time at which to change an initial treatment regimen is obtained from solving a minimization problem.

Chinese medicine

33. Unraveling the mysteries: Mathematical perspectives on traditional Chinese medicine meridians

Chapter by Wei Hu, Xiaoyu Tong, Yu Wang, and Yi Feng [pp. 697–719]

Method Statistical integration of digitized information collected from molecular medicine and pattern recognition techniques in three-dimensional complex spatial structures are considered for integration of traditional Chinese wisdom and modern science.
Application Research for exploration of the structural basis and physiological as well as pathological functions of the nervous, vascular, and endocrine systems in relation to acupoints in the three-dimensional structures of meridians.
Outcome Perspectives are development of mathematical models for meridian-based therapies towards more precise and effective treatments, and model-fusion in quantitative analyses of acupuncture effects.