

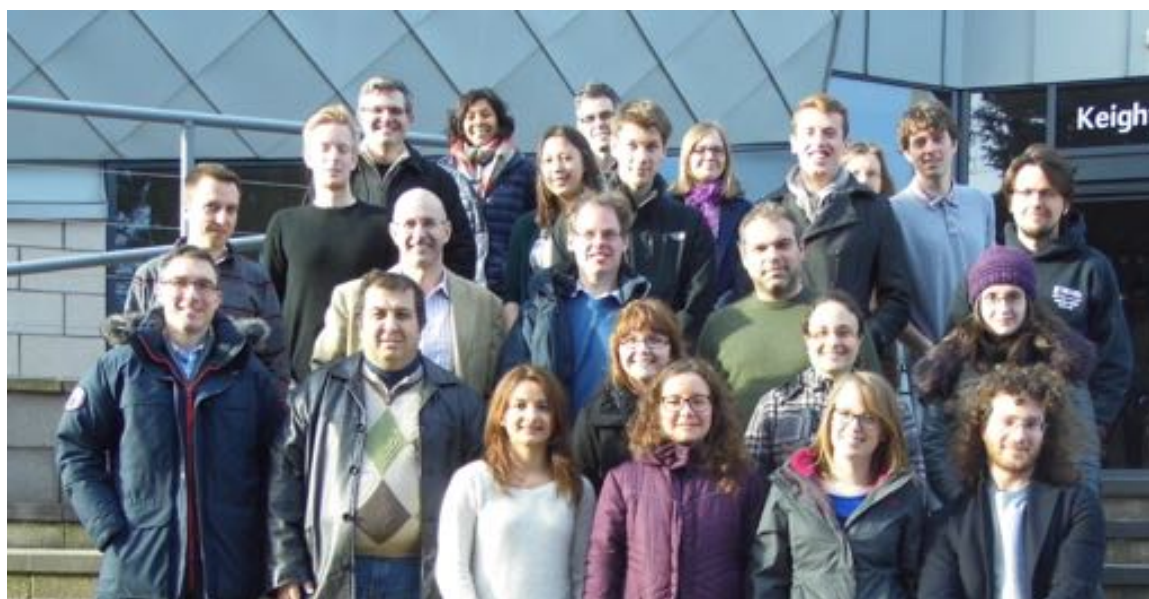
European teams in mathematical biology

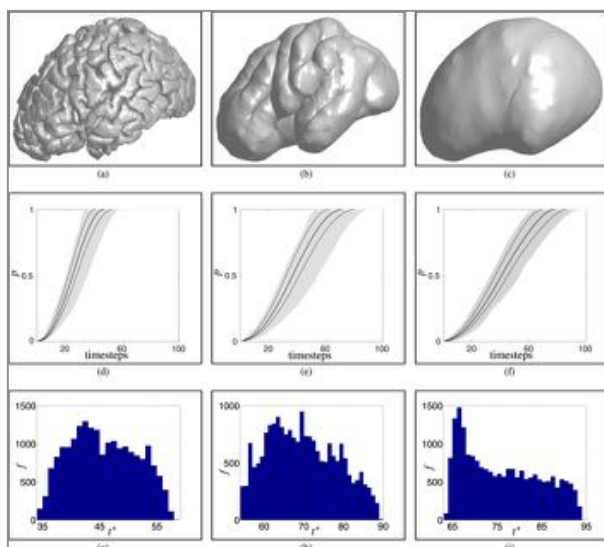
In this issue we begin the presentation of some of the European groups working in the field of mathematical biology.

Centre for Mathematical Medicine and Biology, Nottingham

The Centre is based within the School of Mathematical Sciences at the University of Nottingham, UK. We aim to promote the application of mathematical modelling and statistics to medicine and the biomedical sciences, and to stimulate multi-disciplinary research within the University and beyond. Core members include Markus Owen (Director), Daniele Avitabile, Leah Band, Bindi Brook, Stephen Coombes, Ian Dryden, Etienne Farcot, Matthew Hubbard, John King, Theodore Kypraios, Reuben O'Dea, Philip O'Neill, Rüdiger Thul, Jonathan Wattis and Andrew Wood (full list at: www.nottingham.ac.uk/cmmb/people). Several members of the CMMB are also affiliated with our close partner, the Centre for Plant Integrative Biology (CPIB, www.cpiib.ac.uk).

Our research interests span a wide range of applications including Neural engineering, Synthetic biology (including Biofuels), Biomechanics, Computational toxicology, Drug delivery, Metabolic modeling, Quantitative systems pharmacology, Plant biology and Signal transduction. Many of these applications have important interdisciplinary and industrial impact, resulting in wide collaborative research activity. The nature of these applications often leads to highly nonlinear, complex and multiscale models, necessitating the development and use of a wide variety of mathematical and computational tools within the group. For example, we exploit techniques from scientific computation, statistics, stochastic modelling, multiscale asymptotics, inference and analysis for complex networks, statistical physics and continuum mechanics. Important recent developments include an emphasis on stimulating cross-disciplinary research in Anti-microbial resistance (www.nottingham.ac.uk/bridging), Food security (in partnership with CPIB) and Resource sustainability (including a Leverhulme Trust doctoral training centre: tinyurl.com/UoN-MASS).





The CMMB has historically placed considerable emphasis on developing and supporting the mathematical and theoretical biology community, from initiating Maths in Medicine study groups (maths-in-medicine.org), Maths in Plant Sciences Study Groups and CPIB Summer Schools on Mathematics for Life Scientists, to co-ordinating various UK and International networks ([UK Multiscale Biology Network, 2015-2018](#); [UK Mathematical Neuroscience Network](#); [LMS Mathematics in Life Sciences Network](#); Neural Engineering Transformative Technologies). Since 2009 the CMMB has been an Institute Partner of

the Mathematical Biosciences Institute (MBI) at Ohio State University, USA, and in 2012 we hosted a joint CMMB-MBI Conference on Multiscale Modelling in Medicine and Biology. In a sense this activity will peak this summer when we host the 10th ECMTB (ecmtb2016.org). We are looking forward to many of you visiting Nottingham in July!

Link to CMMB: <http://www.nottingham.ac.uk/cmmb>

CNR IASI BioMatLab, Rome

The Istituto di Analisi dei Sistemi ed Informatica "A. Ruberti" (IASI) of the Italian "Consiglio Nazionale delle Ricerche" conducts research in BioMathematics, Statistics, Combinatorics, Algorithms and Networks, Data Bases, Knowledge Based Systems, Language and Programming theory, Optimization and Operations Research, Pathophysiology, Metabolism and Immunology, Systems and Control Theory. The BioMathematics Laboratory (BioMatLab) is part of IASI: its staff members have core expertise in the fields of biomathematics, statistics, control systems engineering. Its traditional strength has been mathematical modelling and model parameter estimation in biomedicine, including the organization and analysis of clinical trials. CNR IASI BioMatLab operates from within the Catholic University School of Medicine (UCSC) under an institutional agreement between CNR and UCSC. BioMatLab closely collaborates with the UCSC Departments of Surgery, of Anesthesiology and Intensive Care, of Diabetology and Metabolic Diseases, some of whose medical personnel are directly integrated within the CNR research structure.

Our research goal is to help provide reliable quantitative answers to physiological and pharmacological questions. The translation of biomedical problems into workable mathematical formulations, the qualitative analysis of the solutions, the estimation of relevant model parameters from available experimental data and the preparation of fast software tools for model simulation and estimation are our main concern. We mainly work with nonlinear (delayed) dynamical models and stochastic differential equations models. We use population parameter estimation techniques, both frequentist and Bayesian and parameter estimation techniques for Stochastic Differential Equations models. We are specifically interested in estimation and information geometry, as well as in nonlinear observer techniques for

simultaneous parameter/state estimation. Our research has touched several biomedical areas (glucose-insulin system, metabolism of dicarboxylic and medium-chain fatty acids, longitudinal distribution of resistances and compliances in the pulmonary vascular tree, noninvasive assisted ventilation, antimicrobial efficacy, indirect calorimetry, animal embryo development under sublethal toxicants), where we have provided the necessary mathematical and statistical expertise for experimental design, for data analysis and modelling, and for the conduction of multi-center clinical trials.

While the group composition varies a little as time goes by, it essentially consists of bio-mathematicians, statisticians and control engineers. We have also recently extended our activity to legal modelling and ethical analysis and have two JD's in the team. As of 2015, BioMatLab has published about 140 full-length papers on peer-reviewed, international journals. Of these, some are mainly biomathematical, some mainly relative to nonlinear control, some primarily of medical interest.



BioMatLab has participated in several European Projects funded by the EC, most recently under FP7 and continues to be actively searching for funding opportunities both at the national level and under H2020. It has attracted and supported

over the years about 30 doctoral students and post-doctoral fellows, conducting their research at BioMatLab under academic agreements with Italian Universities in Rome or with Mahidol University, Bangkok. BioMatLab has organized or co-organized many European BioMathematics Summer schools.

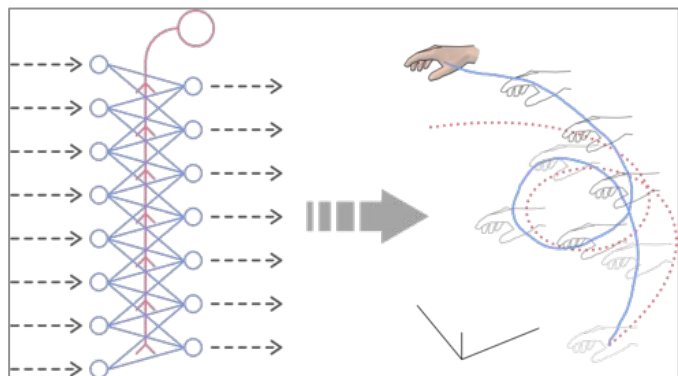
For more details, please take a look at www.biomatematica.it

The Laboratory of Computational Neuroscience, Swiss Federal Institute of Technology, Lausanne (EPFL)

The laboratory is headed by Professor Wulfram Gerstner and has research activities in the area of **mathematical and computational neuroscience**.

The lab is part of the [Brain Mind Institute](#) in the School of Life Sciences and of the School of Computer and Communication Sciences. PhD students at the LCN are part of the EPFL [Doctoral School](#), either in [Neuroscience](#), or in [Computer and Communication Science](#).

Collaborations with experimental groups as well as other theoretical groups are exploited in several projects.



In the lab, mathematical modeling is used in order to understand the role of dynamics for computation in brain-like structures. Dynamics and temporal aspects play a role on all levels

of information processing in the brain. On the neuronal level, aspects of temporal coding by 'spikes', i.e., the short electrical pulses (action potentials) that neurons use for signal transmission are studied by powerful integrate-and-fire models that can be optimized in the framework of Generalized Linear Models. On the behavioral level the research focus is on memory formation as well as spatial navigation in known or unknown environment. On all levels, temporal aspects of learning play a role. Over the years, the lab has developed mathematical models of spike-time dependent plasticity and reinforcement learning as well as novel generalized integrate-and-fire model.



Recent publications include learning in a model of 'Orchstrated synaptic plasticity' (Nature Communications 2015, 6: 6922), transient dynamics for movement generation (Neuron 2014, 82:1394–1406) as well a textbook on 'Neuronal Dynamics - from single neurons to networks and models of cognition' (Cambridge Univ. Press, 2014).

Links:

<http://lcn1.epfl.ch/>

<http://lcn.epfl.ch/~gerstner/>

The Biomathematics Group of the University of Helsinki

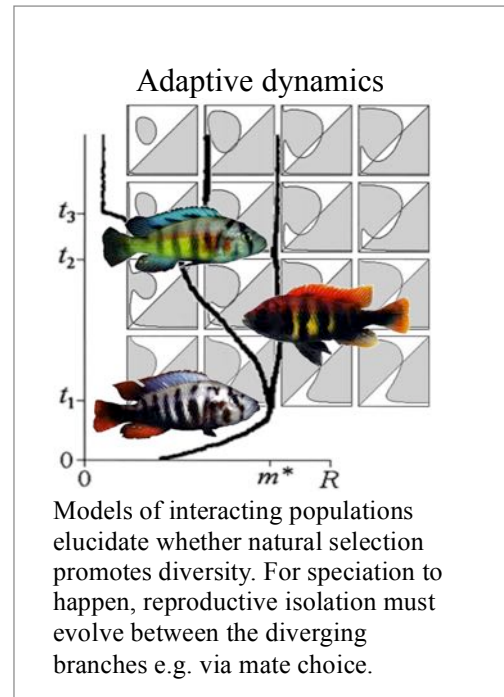
Formed in Turku in 1992, the Biomathematics Group now operates at the Department of Mathematics and Statistics at the University of Helsinki. The group is led by Mats Gyllenberg, its senior members are Stefan Geritz, Eva Kisdi and Ping Yan, and it has attracted postdocs and PhD students from over a dozen countries. Our group is part of the Finnish Centre of Excellence in Analysis and Dynamics.

The group's main interest is in mathematical population dynamics, applied to ecology and evolution. Adaptive dynamics, a mathematical framework for modelling evolution by natural selection in complex ecological systems, plays a central role. Evolutionary branching (see figure) and models of reproductive isolation give insight into the origin of species. We pursue diverse applications of adaptive dynamics, for example to the evolution of pathogens. The intriguing phenomenon of evolutionary suicide demonstrates that "the survival of the fittest" may destroy rather than improve a species.

Our research in population dynamics focuses on structured populations, including metapopulations and dispersal evolution. We develop diverse mathematical methods and numerical tools as needed for problems at hand. We are committed to building mechanistic models, that is, we derive the dynamics of populations explicitly from the underlying behaviour of individuals, and derive evolution from the dynamics of subpopulations with different traits.

The Biomathematics Group runs an international Master Programme in Biomathematics. Our courses

include mathematical modelling, evolutionary game theory, adaptive dynamics, stochastic population dynamics, spatial models and mathematical epidemiology, and we offer publishable thesis projects. We organise symposia both locally (such as regular Biomathematics Days) and internationally, and run the biennial Helsinki Summer School on Mathematical Ecology and Evolution endorsed by EMS and ESMTB.



Group website: <https://wiki.helsinki.fi/display/BioMath/>
 Contact: eva.kisdi@helsinki.fi

The Vienna Biomathematics Group, University of Vienna

Research. Our main fields of research are evolutionary biology, population genetics, ecology, game theory, and cell biology. In particular, we use mathematical models to study how emergent phenomena on the level of populations and ecosystems can be explained from fundamental processes of population genetics (such as selection, mutation, recombination, and migration) and population dynamics (birth- and death processes, interactions among species and with the environment). Current research topics in our groups concern the causes of biological diversity, the analysis of adaptation processes, speciation theory, applications of evolutionary game theory to biology and economics, and cell motility and chemotaxis. Methods include ordinary and partial differential equations, stochastic processes, as well as statistical and computational approaches.

Teaching. *The Master Programme in Mathematics* at the University of Vienna requires specialization to one of seven areas, one being Biomathematics. Therefore, every semester we teach courses and seminars on various topics in mathematical biology. Of course, we also

advise and teach bachelor students and offer a doctoral programme. For details, see <http://mathematik.univie.ac.at/en/study-programs/biomathematics>.



People. Currently, we are five professors (Bürger, Hermisson, Hofbauer, Schmeiser, Sigmund (retired)), five assistant professors or postdocs (Mousset, Peurichard, Polechova, Sasaki, Wittman), six PhD students, and several master students.

Scientific environment. Our group is not only embedded into the Faculty of Mathematics, one of the strongest in Europe, but is also well integrated into an outstanding research environment in evolutionary biology, genomics, and cell biology in and around Vienna (see, for instance, evolVienna: <http://www.evolvienna.at/>). In addition, two of us are PIs in the *Vienna Graduate School of Population Genetics* (<http://www.popgen-vienna.at/>), which is funded by the Austrian Science Fund FWF and offers more than 10 PhD positions in experimental, theoretical, and statistical population genetics.

Additional links:

<http://homepage.univie.ac.at/Reinhard.Buerger/Biomathematik.html>

<http://www.mabs.at/index.html>

Mathematics of reaction networks, University of Copenhagen

Our math bio group in Copenhagen consists of a diverse group of people with very different mathematical backgrounds and training. We work in the area of reaction network theory, which is an area of mathematical biology aiming to understand models of biochemical reaction systems that describe how the amounts of molecular species evolve over time. In our group we are currently nine people, among which there are PhD students, postdocs and professors (see Figure 1).

We are particularly interested in deterministic ODE models arising from the law of mass action or generalisations of it, and their stochastic counterparts, models based on Markov processes (see Figure 2). Though we work on different problems, there are some

mathematical aspects that are pertinent to what we do. We are generally interested in qualitative properties of the models, that is, in answering questions such as: What can be said about the models without choosing specific parameters? What holds generally for all parameter values or for all values in a certain parameter region? As parameters are typically unknown or only known within orders of magnitude, qualitative insight might be useful for designing models as well as for analysing models in connection with experimental data.



As an example of a qualitative property one could mention whether the network is persistent (for all parameter choices), or whether the network admits more than one steady state (for some parameter choices). We approach these questions from a theoretical point of view without relying on simulations and numerical analysis, and we mainly use tools from algebraic geometry, graph theory and stochastic process theory. The network itself can be seen as a graph, and also many, in particular qualitative, properties of a network relate to graphs defined from the network (see Figure 2). This is intuitively as well as mathematically appealing because network properties might be checked by checking properties of graphs and not by analysing equations with many variables and unknown parameters.

Much of our recent work is centred on network reduction. Model simplifications are important in many practical situations, and might also be used to highlight essential components of a network. We find simpler networks that relate in some way to the network of interest and study qualitative properties that are preserved under the reduction. Specifically, we have focused on networks with substrate-enzyme complexes as they appear in many cellular reaction networks and have a rich mathematical structure.

<p>Reaction network</p> $\text{HK} \xrightarrow{\kappa_1} \text{HK}_p$ $\text{HK}_p + \text{RR} \xrightarrow{\kappa_2} \text{HK} + \text{RR}_p$ $\text{RR}_p \xrightarrow{\kappa_3} \text{RR}$	<p><i>Two-component system</i></p> <p>HK: histidine kinase RR: response regulator</p> <p>$\kappa_1, \kappa_2, \kappa_3$: reaction rate constants</p>	<p>DSR-graph</p>
<p>Deterministic model</p> $\dot{x}_1 = -\kappa_1 x_1 + \kappa_2 x_2 x_3$ $\dot{x}_2 = \kappa_1 x_1 - \kappa_2 x_2 x_3$ $\dot{x}_3 = -\kappa_2 x_2 x_3 + \kappa_3 x_4$ $\dot{x}_4 = \kappa_2 x_2 x_3 - \kappa_3 x_4$ <p>x_1, x_2, x_3, x_4: concentrations of HK, HK_p, RR, RR_p</p>	<p>Stochastic model</p> $\frac{dP_i(n)}{dt} = (\kappa_1 n_1 + \kappa_2 n_2 n_3 + \kappa_3 n_4) P_i(n_1, n_2, n_3, n_4) - \kappa_1 (n_1 + 1) P_i(n_1 + 1, n_2 - 1, n_3, n_4) - \kappa_2 (n_2 + 1)(n_3 + 1) P_i(n_1 - 1, n_2 + 1, n_3 + 1, n_4 - 1) - \kappa_3 (n_4 + 1) P_i(n_1, n_2, n_3 - 1, n_4 + 1)$ <p>n_1, n_2, n_3, n_4: molecular counts of HK, HK_p, RR, RR_p</p>	

An example of a reaction network with the deterministic and stochastic models. Properties of the DSR-graph ('directed species-reaction'-graph) can be used to preclude multistationarity or to find positive feedback loops.

Link:

<http://www.math.ku.dk/english/research/spt/reaction-networks/>

Vito Volterra and the beginnings of modern European BioMathematics

Andrea De Gaetano, CNR IASI BioMatLab Rome.

Exploring the life and work of Vito Volterra is an interesting and possibly illuminating experience for us, European biomathematicians. In our everyday life we struggle to reconcile personal themes (children, mortgages, romance, house repairs, vacation planning, dieting, aging parents and the like), hard career issues (paper publishing, grant proposals, departmental politics, unavoidable teaching) and *bona fide* scientific endeavour, the labor and passion of understanding, the excitement of ideation. However busy and frustrated we may sometimes feel, reading about Volterra's life should help us put our troubles into perspective.



Prof. Vito Volterra

Vito Volterra was an extremely gifted mathematician from infancy. He was born in Ancona in 1860, just before the Marche region was annexed to the newborn Kingdom of Italy, of a poor Jewish family. He lost his father, Abramo Volterra, at age 2 and had to contend with the early life of the peripheral, underprivileged, orphaned child. Still, his gift for mathematics enabled him to read Legendre's *Géométrie* at age 11. He attended in Florence the Istituto Tecnico Galileo Galilei (a toned-down, direct employment-oriented version of the Italian high school), where however he was so lucky as to have Cesare Arzelà (of Arzelà-Ascoli theorem fame) as one of his teachers. Following Arzelà, Volterra attended the “Scuola Normale Superiore” in Pisa, an excellence school affiliated with the University of Pisa, where he studied mathematics under the then Director Enrico Betti.

Betti was not only an internationally renowned mathematician (in his honor Henri Poincaré defined a series of topological invariants as “Betti numbers”) and a hero of the Italian War of Independence (he fought at the battle of Curtatone and Montanara in 1848), but also a Member of Parliament and since 1884 a Senator of the Kingdom of Italy. Volterra completed his doctorate in physical sciences in Pisa (anticipating parts of the discoveries in hydrodynamics which shortly thereafter were completed and published by Stokes) and was awarded there a full professorship in rational mechanics, right away: he was 23 years old.

In what we might call the second phase of his life, Volterra covered rapidly a remarkable *cursus honorum*: he taught in Pisa, Turin, then Rome in 1900. He worked feverishly in functional analysis (hence the Volterra functionals and Volterra integro-differential equations) during the golden years of Tonelli, Castelnuovo, Dini and Caccioppoli. He was elected to the *Accademia dei Lincei*, the National Academy of Italy, of which he became President. In 1905 he was nominated lifetime Senator of the Kingdom of Italy. In his political activity he endeavored, among other things, to establish links among European mathematicians, and founded the *Unione Matematica Italiana*, actually as a chapter of the International Mathematical Union rather than as a free-standing national association of mathematicians. He

also worked hard at the establishment of an Italian national research organization, which could concentrate and direct effort towards applied problems of direct usefulness for the Nation, in counterpoint with the rather more theoretical, disaggregated and politicized university system. He believed strongly in the importance of science for social and economic development, in the role of interdisciplinary investigations, in the fundamental contributions that mathematics could offer to developing sciences such as biology, economics and physics.

After the end of World War I (during which he had aided the nation as a volunteer in the newborn Aviation, by developing pointing tables for guns mounted on flying dirigible platforms), right after the accession to power of Mussolini in 1922, Volterra's political trajectory touched its apex. After the creation of the National Research Council of Italy (CNR), in 1923, he was unanimously elected its first President. CNR was to expand the scope of the preexisting *Ufficio Studi e Ricerche*, creating large-scale centralized laboratories and promoting interdisciplinary investigations, with a clear view to transferring research results to industrial applications. Volterra was at this time internationally acclaimed as possibly the most representative figure of the Italian science of those years, and his prestige helped him wage a

bitter opposition to the consolidating fascist regime.

LEÇONS
SUR LA
THÉORIE MATHÉMATIQUE
DE LA
LUTTE POUR LA VIE
PAR
Vito VOLTERRA
Membre de l'Institut
Professeur à l'Université de Rome,

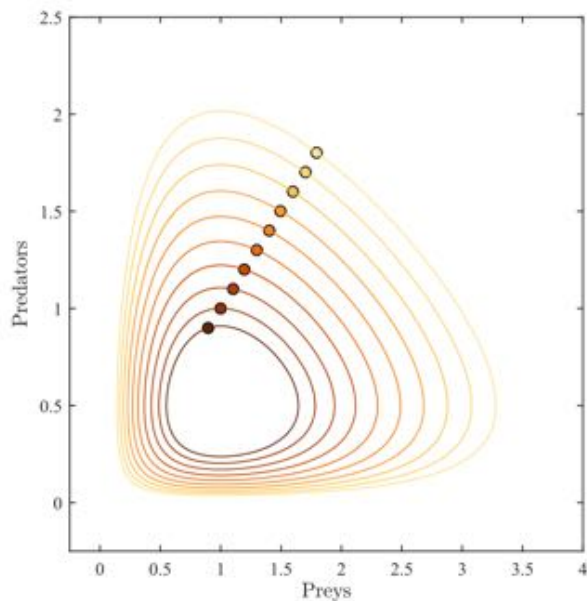
Gautier-Villars, Paris, 1931

The last phase of his life may be thought as beginning when his political opinions led, not unexpectedly, to his removal from the post of President of CNR, in 1927. Incidentally, the man who substituted Volterra as second President of CNR was Guglielmo Marconi, another world-famous Italian scientist, this time of aristocratic birth (Italian

nobleman Giuseppe Marconi his father and English noblewoman Anne Jameson his mother, grand-daughter of the John Jameson Scottish whiskey distiller), and with an English aristocratic wife: Marconi had actually joined the Fascist Party in 1923 and would become member of the Fascist Grand Council in 1930. After the dissolution of Parliament in 1930, the regime in 1931 required all university professors to swear allegiance to Mussolini: out of 1250 professors, 12 refused to swear, among them Vito Volterra, who as a consequence lost his post of Professor in Rome. From 1932 until the end of his life, he spent most of his time in Spain and France. Among his doctoral students, we must remember the French Paul Lévy (martingales, Lévy processes, Lévy measures etc.). In 1936, Father Agostino Gemelli (founder of the Catholic University in Milan, Italy and namesake of the Catholic University's Faculty of Medicine "A. Gemelli" in Rome), promoted the nomination of Volterra as Member of the Pontifical Academy of Sciences in the Vatican: it was this most Catholic academy that organized Volterra's funeral in 1940, in Rome.

It is of interest for us biomathematicians to remember that after the end of WWI, in the early '20s, the young biologist Umberto D'Ancona started courting Volterra's daughter Luisa. Upon evaluating the man's suitability as a possible match, Volterra learned that D'Ancona had been studying the results of fishing in the Adriatic Sea and had observed a remarkable and unexplained phenomenon: during the war, with fishing effort at its minimum, the percentage of predatory fish in the catches had increased. As Umberto and Luisa progressed in the courtship (and eventually married), Volterra developed the coupled equations of his prey-predator system, which was published in 1926, one year after Lotka had published similar equations to explain prey-predator interactions using a plant-herbivore sample system. Progress in the study of dynamical systems representing prey-predator situations under

varying hypotheses was published by Volterra in a comprehensive book in 1931 (*Leçons sur la théorie mathématique de la lutte pour la vie*. Paris: Gauthier-Villars), in French, which started the modern biomathematics field of population dynamics.



Phase plane of Volterra's model

As members of the CNR IASI BioMathematics Laboratory, situated within the Agostino Gemelli Faculty of Medicine in Rome, working every day on mathematical models of medical and biological processes, it is touching for us to read about the life, exploits and defeats of such an intelligent, far-sighted and active predecessor. Some of the problems he was facing, mainly regarding the organization of research and the relationship of research with political power, are still with us. However, applications are flourishing, the field is exciting and biomathematics has affirmed itself as a concrete contributor to our society and well-being. Some of the ideas we can identify from Volterra's life and example, such as interdisciplinary research, trans-national collaboration, and cross-fertilization

between pure and applied research, have proven their value and will in all likelihood continue to do so in the future. The ignorant, insensate waste of life and talent by totalitarian regimes (and corrupted democracies) is an acute loss to us all. It is some consolation to think, as Vito Volterra himself wrote on a postcard he sent in the 1930s, that "*Empires die, but Euclid's theorems keep their youth forever*".

Reinhart-Heinrich Doctoral Thesis Award

ESMTB announces the annual Reinhart Heinrich Doctoral Thesis Award to be presented to the student submitting the best doctoral thesis within the current year 2016 in any area of Mathematical and Theoretical Biology.

Professor Reinhart Heinrich (1946 – 2006) started his research career in theoretical physics and then moved into biochemistry, becoming a full professor and head of theoretical biophysics at the Humboldt University, Berlin in 1990. He is considered a father of the field that is now named Systems Biology, since he investigated various topics such as modelling metabolic networks and metabolic control theory, modelling of signal transduction networks, nonlinear dynamics as applied to biological systems, protein translocation, lipid translocation, vesicular transport, and even DNA repair. Reinhart Heinrich was always searching for the principles that underlie observations, looking for different perspectives and connecting theoretical abstraction with biological evidence. In this way, he inspired numerous students, gave them insight and direction for future research in modern mathematical and theoretical biology, and organized a large number of memorable conferences. Gratefully acknowledging his stimulating support of our interdisciplinary field and, in particular, his way of guiding students and young scientists, the Board of ESMTB decided to offer a Doctoral Thesis Award annually to commemorate Reinhart Heinrich and his legacy in mathematical and theoretical biology.

Prize Awarding Committee includes:

Carlos Braumann

Andreas Deutsch

Philip Maini

David Rand

Stefan Schuster (former assistant to Reinhart Heinrich)

Award

A summary of the thesis receiving the award will be published as the lead article in the 2016 issue of the European Communications in Mathematical and Theoretical Biology. The *award* includes:

- an invitation to present a lecture at the forthcoming triennial ESMTB Conference or, alternatively, a limited travel grant by ESMTB for a scientific visit of the recipient's own choice;
- 1 year's free membership of ESMTB'
- A voucher for Springer books.

Application

Potential applicants may be nominated by any ESMTB member. To nominate a person for the **Reinhart Heinrich Doctoral Thesis Award**, the following information should be submitted to Andreas Deutsch (andreas.deutsch@tu-dresden.de):

1. Name, address, phone number, affiliation, and email address of the **nominator**.
2. Name, address, phone number, affiliation, and email address of the **nominee**.
3. A detailed **statement** describing why the nominee should be considered for the award.
4. An **extended summary** of the thesis (ca. 2-5 pages plus eventual pictures).
5. A **CV** of the nominee in some form.

Closing date for nominations is **30th November 2016**, by which time the thesis should have received final acceptance by the institution granting the doctoral degree.

Shortlisted applicants will be asked to send their full thesis.

CALL FOR MEMBERSHIP FEES 2016/17



<http://www.esmtb.org>

ESMTB membership includes free electronic subscription of the official journal of the Society *Journal of Mathematical Biology* and reduced low subscription rates to the **print edition** (25 Euro) as well as for several other journals.

Please register at www.esmtb.org and send your payment of the required annual dues for 2016/17 by bank draft transfer or electronically (PayPal).

Membership Fees per year:

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- 50 Euro (full member)
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