The new, emerging field of Systems Biology (also sometimes called integrative biology or predictive biology) has gained continuously growing scientific and commercial attention and impact in recent years. The International Conference on Systems Biology (ICSB) has meanwhile established itself as the major international forum in this field. At its inception in Tokyo in 2000 the 1st ICSB attracted approximately 250 scientists. Four years later, the Systems Biology community has more than doubled, so that approximately 800 people attended the 5th ICSB in Heidelberg, the proceedings of which are compiled in this special issue of BioSystems.

Sometimes, the term Systems Biology is used interchangeably with theoretical biology and in silico biology. However, this definition is certainly too narrow because Systems Biology also includes experimental approaches. Having the term in silico on their agenda both the computer industry and the field of Systems Biology appear to share a common law of growing. Both the growth in processor speed and the number of entities stored in GenBank have demonstrated to follow Moore’s law, i.e. they double every 18 months. A similar, or even faster, growth can be observed with Systems Biology. The first textbook (Klipp et al., 2005) and books with contributed chapters (Kitano, 2001; Alberghina and Westerhoff, 2005) on Systems Biology have appeared, and a first book on computational Systems Biology will appear at ICSB 2005 (Kriete and Eils, 2005).

Systems Biology has been defined in numerous ways in recent years. Our objective is definitely not to add another one. We encourage the reader to study these proceedings (and, of course, other literature in the field) and form his/her own definition. Nevertheless, we feel that some introductory comments may be helpful. Systems Biology is about interactions rather than about constituents, although knowing the constituents of the system under study may be a prerequisite for success.

Interactions often bring about novel properties (sometimes called emergent properties), for example, a system may start oscillating although the constituents alone would not. For example, evolutionary biologists have wondered for long how saltatory (jump-like) transitions can occur in evolution. From the viewpoint of systems theory, the answer is easy: by bifurcations. In non-linear systems, at certain points in parameter space, bifurcations occur, that is, a small change in a parameter leads to a qualitative change in system behavior (e.g. a switch from steady state to oscillation). It is clear that the number of potential interactions within a system is far greater than the number of constituents. If only pairwise interactions were allowed, the former number would be \( n^2 \) if the latter number is denoted by \( n \). The number of interactions is even larger if interactions within triples and larger sets are allowed, as is the case in multi-protein complexes.

Over centuries, biologists collected organisms and species, observed, described and classified them. In those studies, the concept of system has played a role as well—the classification was done in a taxonomic system. Accordingly, another term for taxonomy is systematics. However, this is not a system in the sense of Systems Biology because no emergent properties result from it.

The “stamp-collecting” attitude of biology has also been pursued by genomics. This has certainly been a very important and fruitful undertaking and gave us much new insight into molecular biology. However, much of molecular biology is based on reductionism and simple determinism. It is an extreme exaggeration to say that the human genome has been “deciphered”. Besides the fact that not to all ORFs functions have been assigned yet, it should be acknowledged that even if all functions were known, we would be far from understanding the phenomenon of life because knowledge of all the individual gene products does not say much about the interactions.
between them. Cornish-Bowden and Cárdenas (2001) wrote: "a fully sequenced genome is hardly more useful than a list of telephone numbers without all the associated names" (p. 463). Even having the annotated sequence of a genome in hand will not elucidate the way how an organism functions; it is like having the entries of a telephone directory in hand, but not knowing anything about who eats with whom and who sleeps with whom (cf. Shwed, 2001).

Systems Biology has many roots, some of which being very old. Some of the ancient Greek and Chinese philosophers had put forward systemic ideas. In modern times, Capra (1974) argued that a system’s view of life is important and that we can learn a lot from Eastern philosophy where the main terms have connotations of dynamics and interactions. This is of interest for modern physics (e.g. string theory) and also for modern biology, for example, in realizing that functions can be assigned to genes only if their interactions are considered. Systems approaches to chemistry and biology had also been put forward by Erwin Schrödinger, Alan Turing and Ilya Prigogine (cf. Westerhoff and Palsson, 2004). Elaborating on Turing’s ideas, Gierer and Meinhardt, (1972) developed their models of morphogenesis. Even if these models are controversially discussed until now, they were an early effort in systemic thinking in biology. A field in which systems analysis is intensely used, for example, in enzymology when enzymes are purified and studied in isolation from other enzymes. A decomposition into functional entities (sets of enzymes operating together) is made in Metabolic Pathway Analysis (cf. Papin et al., 2004). However, many systems properties cannot be understood by decomposition. Consider, for example, a ship made of steel. If we wanted to understand why it is able to be afloat, we should not decompose it. Each steel plank cannot be afloat while the entire ship can. Here, a holistic approach is needed. Another frequently instrumental approach is approximation. However, if we have a leaky balloon we cannot say the balloon would be approximately sealed (that is, we could neglect the small leak). The leak will imply that the balloon cannot be observed in a round shape. This shape is a systemic and in a sense holistic property.

In the evening lecture entitled “Systems Biology—a user’s view” at the eve of ICSB 2004, Yuri Lazebnik asked the question “Can a biologist fix a radio?” (see also Lazebnik, 2002). His entertainingly phrased ideas have very profound implications. First, they show that the classical single-knockout approach of geneticists is insufficient (knocking out a transistor and observing that the radio is not functioning anymore does not tell us what the exact function of the transistor is). Moreover, drawing a diagram indicating which component influences which one, as often done in studies of signal transduction, is insufficient. It would not explain the functioning of a radio. To that end, at least the special diagrams of electric engineering are needed and, in fact, a lot of mathematics. One of the major goals in Systems Biology is now to find appropriate ways of diagramming and mathematically describing the specific, complex interactions within and between living cells. (Sometimes the schemes of electric circuits have been transferred to biology, but without much success). For example, mathematical modelling helps predict the point of no return in apoptosis (cell death) (Bentele et al., 2004; Eissing et al., 2004).

Although no contribution in these proceedings deals with game-theoretical approaches, we believe that such approaches will be very helpful for Systems Biology. The interaction between species can be modelled as the interaction between “players” in the sense of game theory. A particularly interesting setting is the Prisoner’s Dilemma (cf. Axelrod, 1984), in which the situation of cooperation is left due to the tendency of two players to increase their profit (e.g. fitness of species), which leads to a decrease of the profit of both players (again a counter-intuitive result). Such situations of “arms race” decomposed into smaller units. This approach is used, for example, in enzymology when enzymes are puriﬁed and studied in isolation from other enzymes. A decomposition into functional entities (sets of enzymes operating together) is made in Metabolic Pathway Analysis (cf. Papin et al., 2004). However, many systems properties cannot be understood by decomposition. Consider, for example, a ship made of steel. If we wanted to understand why it is able to be afloat, we should not decompose it. Each steel plank cannot be afloat while the entire ship can. Here, a holistic approach is needed. Another frequently instrumental approach is approximation. However, if we have a leaky balloon we cannot say the balloon would be approximately sealed (that is, we could neglect the small leak). The leak will imply that the balloon cannot be observed in a round shape. This shape is a systemic and in a sense holistic property.

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are indeed found in biology, even at the level of biochemical pathways (Pfeiffer et al., 2001). A common dogma says that the whole is more than the sum of its parts. In a Prisoner’s Dilemma situation, the whole can be worse than the sum of its parts.

It should not be neglected that there are critical voices concerning the new “hype” of Systems Biology. Interestingly, it is exactly one of the pioneers of this discipline – Fritjof Capra – who warns us not to be overly optimistic (Capra, 2002; cf. DeFrancesco, 2004). In the 1990s, when the field of Bioinformatics has been established, many hopes were put into that field. Bioinformatics was (and still is) supposed to help create new drugs against old, severe diseases, develop personalised medicine, boost bioengineering, and so on. These hopes have not been fully satisfied yet. The number of newly developed pharmaceuticals per year has hardly increased in spite of the enormous efforts spent. Now many people say that bioinformatics alone could not do the job because it is too much oriented towards analysis, and that systemic approaches are needed. We agree with that opinion, but we also feel that warning voices should be heard as well. We are optimistic that fascinating and stimulating new insights will arise from Systems Biology.

Based on the inherent interdisciplinary nature of Systems Biology, this Special Issue of BioSystems covers a broad range of biological fields, as well as methodologies from the computational and life sciences. According to a well-accepted tradition, the ICSB 2004 programme committee has coined a motto for the conference in 2004: “Systems Biology—from Bioscience to Medicine”. Following this guideline, session topics for the conference were chosen that encompass the understanding of Metabolic and Signal Transduction Systems, Microbial Systems Biology, Methods and Software for Systems Biology, Spatial Models, and Systems Biology for Medicine. Contributions from all these sessions are included in the proceedings. We feel that the present special issue provides a representative overview of recent achievements in Systems Biology. Medically relevant topics such as cancer research and enzyme deficiencies are treated. Moreover, signal transduction, Metabolic Pathway Analysis, the dynamics of metabolism, metabolomics, parameter estimation, spatiotemporal modelling, nanobiomechanics, protein–protein interactions, microbial ecology, and computational aspects (techniques for whole-cell modelling) are covered. Several papers deal with combined modelling and experimental studies, thus showing the mutual stimulation of these approaches.

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