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Weak Links

The Universal Key to the Stability of Networks and Complex Systems

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To the memory of my parents

Preface

Since the publication of the first edition of this book in 2006, network science has become a centerpiece of our modern thinking. This is true not only for our scientific efforts to understand the daunting complexity of biological and technological data, but also for everyday life. Barabasi's excellent book on networks *Linked: The New Science of Networks* (Barabasi, 2002) has been translated into eight languages, while *Tipping Point* (Gladwell, 2000) has long been a bestseller in all lists, and the term 'netocracy' (Bard and Söderquist, 2002) has become a key word in our understanding of how to become influential in a modern, networking society.

Networks have gained a novel importance in the monetary and economic crisis which broke out in 2008, and it has become rather clear that, without a more detailed knowledge of economic networks, we will not be able to predict the outbreak and spread of economic turmoil. Thus, network knowledge is a key asset when planning immediate counter-measures against crisis. However, we also have to reflect on long-term remedies. Without a better knowledge of social network stability, without a proper, network-based development of social capital, we will not be able to prepare a crisis-resistant society.

In order to prepare for the job of long-term crisis management, a great deal of effort has been made over the last 2–3 years to understand the finer structure of networks. Network communities, modules, and their overlapping regions have become a hot issue. Network scientists often speak about 'bridges', 'bottlenecks', and recently, 'brokers'. Besides this, the understanding and modeling of dynamical changes in network structure are of extreme importance (Palla et al., 2007). Network analysis has also enabled us to construct algorithms that can predict network behavior (Clauset et al., 2008). Besides economic and social networks, these novel network tools help us to analyze the heretofore rather unexplored complexity of disease and drug networks (Spiro et al., 2008), in the hope of finding novel cures for many life-threatening diseases.

Exploring the complexity of large networks with many millions of elements and even more links has given us a novel understanding of the weak link concept. We have at least two classes of weak links. The long-range, intermodular bridges are the weak links in the original sense of the Granovetter concept, as described in detail in Chap. 1 of the book (Granovetter, 1973; Kossinets et al., 2008). These long-range links connect distant sites of the network, and constitute a small, but very important segment of weak links. These bridging contacts often give us novel information, and may make someone influential, a modern-day 'netocrat' (Bard and Söderquist, 2002; Burt, 1995).

An even more exciting subtype of weak links not only connects distant network regions, but dynamically changes its position from moment to moment. Network elements forming these transient, long-range links often behave as creative elements (Csermely, 2008), playing a key role in the development, survival, and evolvability of complex systems. Creativity is a luxury of any system in business-as-usual situations. Creative elements are not reliable, since – rather annoyingly – they always discover a novel solution. However, this nuisance becomes a life insurance whenever an unexpected situation or crisis crops up. In these extraordinary moments, the survival of the whole community may depend on the existence and mobilization of their creative elements. We find creative elements as active centers in proteins, as stress proteins in cells, as stem cells in our body, very likely as all neurons in the brain, and last but not least, as creative people or groups in our society. I have inserted a new section (Sect. 2.3.2) to describe in detail the help provided by these special, creative network elements in crisis management.

The vast majority of weak links are not from the 'creative links' mentioned above. They are just simply transient, low affinity links, and they are weak. However, their weakness constitutes the majority of links in most networks. The diversity, the vast resource of the myriads of weak links, provides for the extremely important buffering capacity of complex systems, which increases their robustness and chances of survival in times of danger and crisis.

The economic crisis started in 2008, and is often described as an over-consumption crisis in long-range, broad terms. The measures to minimize the effects of over-consumption, i.e., to slow down climate change and to save the diminished resources of our planet, often include a search for alternative energy and other alternative resources. We may indeed need alternative resources. But what we need a thousand times more is an alternative lifestyle. This alternative lifestyle will not focus on our consumer benefits and goodies, but will build a loving and caring social network around us. I hope that this book gives the reader adequate advice for changing her life to be compatible with the needs of our planet and to enjoy a lot more personal and spiritual enrichment at the same time.

Weak links gave me a tremendously joyful experience after the publication of the first edition of this book. The LINK Group received hundreds of emails from all around the world. As an example we made significant progress in understanding creative behavior in the development of cooperation (Wang et al., 2008), working together with a colleague, Shijun Wang, although we never saw each other in person over the last 3 years. I attended hundreds of public lectures on networks and our modern, alternative lifestyle.

Let me close this preface with two emails I received from a boy and a girl in a Budapest high school at the end of 2008:

> Peter, following your advice I started to talk to a complete stranger after your lecture in our school. Imagine!!! A miracle happened! Eve, who is a beautiful girl, found me a perfect match, and we have been together from then on. Peter, without your lecture I would now be an unhappy man.

> Peter, after your lecture I promised to follow your advice, and gave a bright smile to everyone I came across on my way home. I felt as though I was living in a completely different town! You will not believe this! People smiled back! Two of them even started a very friendly conversation with me. I no longer feel myself alone in this huge city. The streets are full of people who are just waiting for our smiles.

Yes, the streets are indeed full of people who are just waiting for our smiles. Weak links give us hope and strength to survive the crisis, and to discover a novel life for tomorrow. How can we do this? Start reading! And write to us if you need any weak links beyond those in your huge (or not so huge) city.

Budapest, Hungary
February 2009

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Preface to the First Edition

In 1990 I started to work with molecular chaperones as an ordinary biochemist. Chaperones are the proteins that form our cells' most ancient defense system. I found them fascinating molecules. They protect other proteins and, consequently, help our cells to survive. If we quarrel, if we are anxious, or just run our daily marathon to catch the morning bus, our proteins become damaged. And damaged proteins are sticky. They aggregate, which is toxic to the cell. Chaperones protect these damaged proteins against unspecific, unplanned aggregation, like their eponyms, the ladies at the grand ball, who would protect young girls against unspecific, unplanned aggregation with the boys at the ball. Chaperones are everywhere. They are needed for protein folding and refolding, for proteolysis and transport. Chaperones are highly conserved and form a part of the essential gene set (Koonin and Galperin, 2002). Without them, no life could be imagined on Earth.

Chaperones are truly altruistic. They help, wherever they can. But how do they help? This was my first question. For five years I tried almost everything an ordinary biochemist could do. I purified them,[1] I cut them into pieces, cooked them and soaked them in an arsenal of chemicals and radioisotopes. By the middle of the 1990s, I realized that chaperones are different. They stick. They bind to their target proteins, their modulator proteins, the cytoskeleton, the whole world. If chaperones glue the whole cell together, how can it change? How do cells divide and how do they move?

The secret is affinity. Chaperones make *low* affinity interactions with their partners. Now they bind it, now they don't. They are dynamic. For their omnipresent help, they form weak links which change often. What makes life easy for the cell is a headache for the resear-

[1]Footnotes will refer to additional information which is not needed to understand the main text. Therefore the reader may skip them. The first footnote is about the word 'purification'. We biochemists use this word for the procedure whereby we cut all original contacts of the protein and extract it from natural conditions, hoping and believing that it will remain unchanged.

cher. Most of the chaperone complexes change if you start to examine them. Now you see them, now you don't. Chaperones give the ordinary biochemist nightmares. It is better to change subject if you want to use your usual assays in a sensible manner. I did not change subject – so the subject changed me. In 1990, I was looking for a well-defined question, and instead, I found a whole world with an astonishing complexity.

In 1998 a seminal paper by Suzanne L. Rutherford and Susan Lindquist appeared in Nature. The take-home message was that one of the chaperones, Hsp90, helps developmental stability. If this chaperone works, almost all the *Drosophilas* look alike. Each of these fruit flies gazes at the world with two complex red eyes, uses six small legs to balance her fragile body, and has two wings, which buzz in unison. If the Hsp90 was damaged, the newly born fruit flies went crazy. Fortunately, not all ten thousand of them did get damaged. Most of the flies still gazed, balanced and buzzed alike. However, *some* of them (exactly 174) became frightening monsters. These poor flies did not have correct eyes, their wings got distorted, their legs were deformed and a number of other malformations also occurred. Indeed they looked pretty miserable. But, miserable in *different* ways. An astonishing diversity appeared, and what is more, this diversity was inheritable. This was due to a variety of preserved silent modifications in the genome of the *Drosophila* population. Normally, Hsp90 buffered these changes and stabilized the appearance of the fruit flies, the phenotype. When Hsp90 was inhibited or damaged, the buffer diminished, and a burst of diversity suddenly appeared.

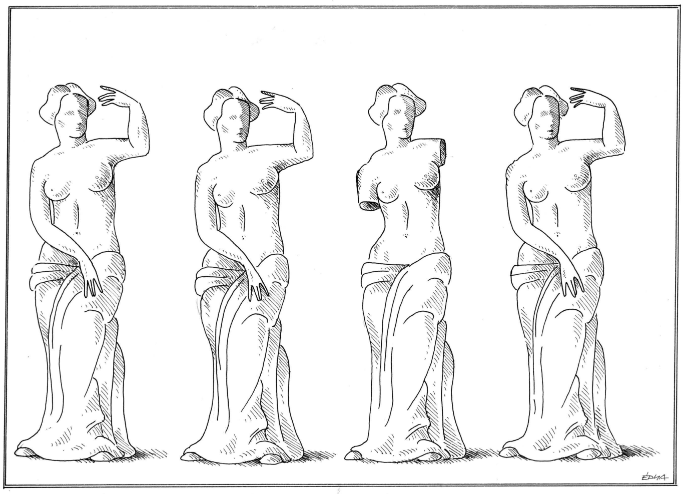
I got the feeling that something truly new had happened. Chaperones help the proteins around them. I could not figure out exactly how they do this, but at least I had an idea: chaperones bind to their target proteins and stabilize them or change their shape. But how can they stabilize a fruit fly, which is much bigger than them?

The explanation I offered myself was still quite standard, saying that chaperones repair mutant proteins which cannot exert their effects on the phenotype. Hsp90, the chaperone in the Rutherford and Lindquist (1998) experiments has hundreds of client proteins which always require its presence for their activation. Most of these clients participate in various steps of signal transduction. Let us suppose that the gene of one of these client proteins suffers a mutation, and that the mutation changes a critical amino acid and cripples the shape of the protein. Let us also suppose that Hsp90 is able to repair this damage, and that, if Hsp90 operates at full strength, the effect of the mutation is not seen. Finally, let us suppose that the client protein was critical in a signaling pathway of the morphological development. If Hsp90 is damaged, the mutation will impair the client. The missing client causes a collapse in morphological signaling and the fly will become a monster. The explanation seemed to be rather easy. (Well, it was easy for us, but not for the fly.)

There were disturbing signs though. Chaperones were not the only things that could hide the monsters within some of the normal *Drosophilas*, who seemingly gaze, balance and buzz just like their peers with a normal genome. There were numerous other proteins, which provided the same buffering, either in this or in other experimental systems (Aranda-Anzaldo and Dent, 2003; Gibson and Wagner, 2000; Scharloo, 1991; True and Lindquist, 2000). Moreover, in 2003 it was proposed that an astonishingly large number of proteins could regulate developmental stability (Bergman and Siegal, 2003). I became puzzled. I found chaperones fascinating. I loved them, and love always carries us to extremes. We see our beloved everywhere. Everything reminds us of her, she is everywhere. But wait a moment! Most of the proposed proteins had nothing to do with chaperones. Chaperones turn up here and there. But the whole cell cannot be a chaperone! The old explanation was clearly not adequate.

I think I am lucky. When one meets the unexpected, a fresh mind is needed, which finds an immense joy in each playful new thought. There are exceptional people, who have this even in their eighties. There are others, who are lucky enough to be stimulated by others. I started a project in 1996 giving research opportunities for high school students (`http://www.kutdiak.hu`). This movement changed the life of many students, and changed my life too. The students in my lab helped me to take a new look at the world. They were the seeds of the LINK group, who helped to write this book.

Let me put things together again. Rutherford and Lindquist (1998) showed that chaperones buffer the morphological diversity induced by the silent mutations of fruit flies. The inhibition of numerous other proteins can also lead to morphological diversity. However, there was something else here. Rutherford and Lindquist (1998) also demonstrated that stress induces a broader morphological diversity. In fact, the stress-induced, prolonged increase in morphological diversity was first shown by Schmalhausen and Waddington much earlier (Schmalhausen, 1949; Waddington, 1942; 1953; 1959). At first, I did not take much note here. It all seemed rather easy: perfect flies are alike, while stressed flies become damaged, *differentially* damaged. Diversity is revealed in the damage. At the molecular level, stress means more damaged proteins. Chaperones try to repair them, and so become occupied, which is just another form of inhibition.



Diversity is revealed through damage

In May 2003, I happened to read the review by Rao et al. (2002). This opened a new world to me. Stress not only induces morphological diversity, but also a thousand other types of diversity. Each bacterium normally swims towards its food. But not when stressed! Here, some of them got really distressed, and either swam in the opposite direction, moved round in circles, or just didn't go anywhere. Here we have diversity again. *Bacillus subtilis* responds to environmental stress with an arsenal of probabilistically invoked survival strategies. Stem cell differentiation or the appearance of various types of cancers can all be a source of similar diversity. Can all these forms of diversity be buffered by chaperones?

Putting this together, we are bound to ask: do we have here a large number of mysterious proteins which stabilize practically everything? This is the time when one goes for a vacation or asks around. As I was too excited to go for a vacation, I wrote to some of my best friends (I can imagine their faces as they stared at their laptops: "Peter went really crazy this time ...") – and got back some great ideas. Tamas Vicsek suggested that I read the recent book by Laszlo Barabasi on networks (*The Linked*, Barabasi, 2002). In parallel, I started to read *Investigations* by Stuart Kauffman (2000). These were the best books I had read for quite a while.

Then I had to sit down. Practically every complex system can be imagined as a network. Atoms form a network making macromolecules. Proteins form a network making cells. Cells form a network making organs and bodies. We form a network making our societies, and so on. Most of these networks are a result of self-organization. In fact, self-organization seems to be an inherent property of matter in our Universe. The resulting networks have a lot of common features, from their topology to their dynamism.

These systems are far too similar. The protein net, where chaperones work, should behave in the same way as every other network. *All* networks must have a component which stabilizes them, like chaperones and the mysterious proteins stabilizing the cells. But what is the common feature of all these elements? Why do they stabilize the whole network? At the beginning I had only one idea, and even this was negative. The common feature *cannot* be anything related to chaperone function. Chaperones protect other proteins by helping to refold them. People cannot protect their friends by helping to refold them! A more general approach is needed here.

Although I did not know it, the solution was already in my hands. Chaperones should give us a clue. Which of their features can be generalized to *all* networks? Chaperones stick. They make links to a number of other proteins. They are hubs. Do hubs stabilize their networks? Well, not really. Hubs are needed to *form* their networks. If we attack hubs, the network collapses (Albert et al., 2000). When we attack chaperones, the network, e.g., the cell survives. It becomes destabilized, but survives. Another chaperone feature must be more important.

What else? Affinity! Yes, affinity. Here was an idea: *The components which stabilize the various systems must all have weak links to the others*. It is not the component that counts, but the type of link it builds to the others. By the end of 2003, the basic idea of this book was born: weak links stabilize all complex systems. Weak links give us a universal key to understanding network diversity and stability, and they are the major actors in this book.

Months of tedious, systematic reading followed. I read dozens of books, collected approximately 600 Mbytes of pdf files, which made a pile of printed hard copies three meters high. I realized that my ‘new’ idea (weak links stabilize all complex systems) has been an obvious feature in the social sciences for decades (Granovetter, 1973). The same idea had been proven in ecosystems in 1998 (Berlow, 1999; McCann et al., 1998). As I browsed page after page, many other examples appeared, and they will be detailed in the following chapters. This made me rather confident that I had found something genuinely important and general. Interestingly, many authors (like Mark Buchanan in his book, *Nexus*, 2003) had come to the conclusion that weak links stabilize complex systems in their own discipline, but none of them had generalized it to all networks.[2] It seems that it was the chaperones, which stick but form only *weak* links, that had made the important link here.

While I was reading one book after the next and paper after paper, I got more and more surprises:

- I realized that each of the disciplines has a completely different vocabulary for the very same message. (Appendix B is a glossary intended to guide the reader through this jungle of terminology.)
- It was a frightening moment when the LINK group realized that we had completely run out of words and had no way of talking about something so truly simple and beautiful. But let me reassure you: the book is not full of newly constructed pseudo-words. We always managed to get around the problem ourselves and find a novel use for some existing word. However, on many occasions, it took us some time. When one has to use words in a completely different context, one's mind seldom obeys at first.
- The readings gave me a great and sincere respect for the social sciences. In network studies they are a whole lifetime ahead! Jacob Moreno started network studies on friendship patterns and Alfred Lotka published his famous law on scientific productivity in 1926, when my father was born. Anatol Rapoport stressed the general importance of the topology of friendship networks in 1957, one year before my own birth (Newman, 2003).

The book is structured as follows. In Chap. 1, I describe the beginnings of the weak link concept, the Granovetter study, and define weak links. Chapters 2 and 3 summarize the description and dynamics of networks. Chapter 4 introduces the concept of weak links as universal stabilizers, while Chaps. 5 through 11 invite the reader on a journey through Netland, presenting a ladder of exciting examples starting from macromolecules and ending at our own planet. Finally, Chap. 12

[2] The following remark by Siljak (1978) counts as another predecessor of these thoughts: "A dynamic system composed of interconnected subsystems is reliable if all subsystems are self-sufficient and [...] the magnitude of the interactions does not exceed a certain limiting value." This statement may be regarded as a forerunner of the main thesis of this book, but Siljak's stability criterion can be formulated much more easily using the concept of networks as it is presented here.

summarizes and reformulates the stabilizing role of weak links, bridging it with the concept of stability landscapes and game theory. If you dislike physics or the biochemistry of small molecules, feel free to start your journey in Netland at Chaps. 7 or 8, which describe the networks of our own body and our societies.

When the first draft of the book was finished in January 2004, I realized that I had probably filled a niche. According to Newman (2003): "Studies of the effects of structure on system behavior are still in their infancy." Cross-disciplinary thinking on network properties is also largely non-existent. The moral is that we should use this enormous resource more often, always examining what we have proved in one of the disciplines when it is transferred to all the others. I have done my best. However, I am aware that analogies provide a very fruitful but extremely dangerous field. Therefore I will separate the analogies from the established facts by quoting the original source of information after each fact and by putting most of the analogies into a box in the following manner:

Caution! Hypothesis! As you proceed in the book, wild ideas will appear along the way. I expect a good deal of red ink from the referees: "Speculative!" But I have an excuse: I have *marked* all these hypotheses using one, two or three of the smiley figures on the left. The figure has big hands as a reference to the great Hungarian magician, Rodolfo, who always said: "Watch my hands! Caution! I am cheating!" One smiley means that I do not have enough evidence to formulate the statement as unequivocal truth. Two smileys warn you that, though the statement is logical, its background is largely missing. And three smileys? Well, three smileys will make you either smile or run to the phone to call the doctors in white coats. Three smileys are mostly fiction, rather than science. So why did I put them in this book? They have dared to appear here because they constitute fascinating, mind-boggling ideas. Smiley comments will always be exciting, but I am not quite sure that they will turn out to be true.

Additional information. Those parts where you find the wise head on the left will most probably turn out to be true tomorrow, and even the day after tomorrow, but they are details that will not necessarily interest all readers. Start reading, but if you do not find it interesting, skip it.

Important questions. When you begin to study a new territory, you always have more questions than answers. (In fact, a good scientist *always* has more questions than answers.) So we wondered why we should keep these questions to ourselves, and we decided to share. If you have a good idea for an answer, we would be more than pleased to read and discuss it. Join the LINKs! The email address is at the end of this Preface.

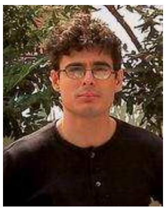
My master's voice: Spite. Sometimes you will see a remark in the text like: ***"Peter, you made the typography of this book rather confusing for me. First of all, I cannot read your small letters in the remarks. Moreover, the font you selected for me is the ugliest one I have ever seen."*** Spite! Welcome! Spite is my best friend. When you try to write a book, your best friend is the most critical person around you. I am lucky enough to have quite a few such fierce critics among my students.

Some of the sentences in the above remarks were written in the plural. What has happened? Does the author think he has found such a good idea that he may start to speak in the plural, as if to say: "We, the founders of this new science, declare ..."? Not so! The more 'we' know, the more humble 'we' grow. 'We' refers to the members of the LINK group. The LINKs are young people (at least in mind!), who work in different institutions but are strongly linked to each other by their love of weak links and decided to form a virtual lab. Members of the LINK group helped to shape this book. They sent great ideas to each other by emails, by SMS messages and even on slips of paper. Questions arose sometimes during the day, sometimes during the night. The LINKs attacked the sloppy sentences of this text and tried to make the content of the book more understandable. We all hope that this joint effort has brought at least a little improvement. If not, please send all your comments to us. Here are some of the key people in the LINK group:

Péter Csermely left the János Apáczai Csere high school in Budapest, Hungary in 1976. He is now professor at the Semmelweis University in Budapest, Hungary. He has published 11 books and two hundred research papers with more than 3 500 independent citations. He started a project in 1996 providing research opportunities for more than 10 000 high school students in the best research teams (www.kutdiak.hu). In 2006 he established a nationwide talent support program in Hungary and was asked to participate in the Wise Persons' Council by the Hungarian president. Among other honours he received the Descartes Award of the European Union in 2004.

István Kovács left the János Berze Nagy high school in Gyöngyös, Hungary in 2003. He won awards in more than a dozen national physics and mathematics contests. He is currently a physics PhD student at the Eötvös University of Sciences in Budapest, Hungary. He published his first scientific paper at the age of 19.

Balázs Papp left the high school of the Debrecen University, Hungary in 1996. He received his MSc degree in genetics at the Debrecen University and his PhD from the Eötvös University in Hungary. He is currently establishing his own lab at the Biological Research Centre in Szeged, Hungary. He has published three papers in Nature, won several honors and awards including two Marie Curie Fellowships and a Pro Scientia Medal.



Csaba Pál left the István Dobó high school in Eger, Hungary in 1993. He received his MSc and PhD degrees from the Eötvös University in Hungary. He is a group-leader in the Biological Research Centre, Szeged. He has published three papers in Nature, one in each of Nature Genetics, Nature Reviews in Genetics, and Science, as well as six papers in various Trends journals. He was a Royal Society Postdoctoral Fellow and won the Talentum Award of the Hungarian Academy of Sciences in 2005.

Máté Szalay left the László Lovassy high school in Veszprém, Hungary in 2003. He was the recipient of the 2003 Junior Bolyai Award of computer science. Between 2003 and 2005 he was the president and later the managing president of the Hungarian Research Student Association (`www.kutdiak.hu`). He is currently a computer science undergraduate at the Technical University in Budapest, Hungary.

An interdisciplinary subject is always dangerous. One cannot know, and cannot even understand everything. In spite of this, writing about weak links must not mean weak writing. I owe a lot of thanks to the eminent scientists of various disciplines, my friends, who read the summary of this book or its chapters. I am thankful for their comments, ideas and encouragement. The help of Luigi Agnati, Eszter Babarczy, László A. Barabási, Attila Becskei, Eric L. Berlow, Gustav Born, Zoltán Borsodi, Geoffrey Burnstock, György Buzsáki, Vilmos Csányi, Ken Dill, Gerald M. Edelman, András Falus, Viktor Gaál, Balázs Gulyás, Mária Herskovits, Gergely Hojdák, Roland Iványi-Nagy, Gáspár Jékely, Ferenc Jordán, Márton Kanász-Nagy, Katalin Kapitány, Mária Kopp, Steve LeComber, Leon Lederman, Susan Lindquist, László Mérő, Ágoston Mihalik, István Molnár, Viktor Müller, Zoltan N. Oltvai, Kleopatra Ormos, Bálint Pató, Csaba Pléh, Zoltán Prohászka, Ricard V. Solé, Csaba Sőti, Attila Steták, Steven H. Strogatz, András Szabó, Péter Száraz, Gábor Szegvári, Attila Vértes, Tamás Vicsek, Denise Wolf and Peter Wolynes is gratefully acknowledged.

Without the encouragement of Tamás Vicsek, the help of our librarian, Csilla Szabó, and last but not least the editorial team, Claus Ascheron, Adelheid Duhm, James Fuite, Angela Lahee, Stephen Lyle and Jack Tuszynski, this book could not have been written. I would like to thank to all members of my family and my colleagues for their understanding during the writing process. Finally, let me introduce Édua Szűcs, to whom I am extremely thankful for the excellent artwork in the book.

Édua Szűcs left the Miklós Radnóti high school in Szeged, Hungary in 1977. She received her MSc from the Szeged University, Hungary. Starting her independent art work as a cartoonist in 1986, she has had more than thirty exhibitions in Hungary and abroad. Her published works include Edua cartoons (1997), Edua cartoons 2 (2001), and illustrations for several books. Awards: Szféra special awards (1996, 1999); Karikatórium special award (1997); Foundation for Hungarian Culture Award (1998); Women for the European Union, first prize (2003).

At the end of this preface, let me invite you once again to send us comments and questions. The LINK group can be reached at the following address and website:

`info@linkgroup.hu` `www.linkgroup.hu`

Budapest, Hungary *Peter Csermely*
September 2005

Contents