ICE-like predilection for cleavage after aspartate residues and trigger apoptosis). Although it is tempting to place CPP-32 near the apex of a proteolytic cascade leading to cell death, a strict hierarchy may not exist: rather, different family members may operate in different tissues or act on differing substrates within an individual cell to trigger apoptosis.

Of course, many questions remain. One concern is that the Yama/CPP-32 of Tewari *et al.*[2] shows far greater sensitivity to inhibition by CrmA than the apopain/CPP-32 activity of Nicholson *et al.*[1]. The reason for this discrepancy is unclear, but the possibility arises that the two activities are properties of different polypeptides. From a mechanistic stance, the most intriguing questions must be what does CPP-32 actually do to trigger apoptosis, what are its substrates and the consequences of their cleavage, and does active CPP-32 trigger a final and ineluctable process of apoptosis, or is reprieve still possible? On this last question, the jury is still out. The genetic interactions between the nematode *ced-9* 'anti-death' and *ced-3* 'death' genes (and, *mutatis mutandis*, *bcl-2* and CPP-32) provide no real information as to the biochemical relationship between these two proteins: Bcl-2 could act either upstream or downstream of CPP-32. Nonetheless, Bcl-2 expression does suppress ICE-induced apoptosis[4], as do survival signals[4,7,12], implying possible modulation of CPP-32 action.

Indeed, a bewildering diversity of factors influence apoptosis — not only cytokines and Bcl-2 family proteins, but extracellular matrices, oncogenes, tumour-suppressor genes, DNA-damaging agents, and elements of the cell-cycle machinery. Quite how all of these affect the actions of CPP-32 and related proteases remains part of a much larger mystery, as indicated by the profusion of question marks in the figure. □

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1. Nicholson, D. W. *et al. Nature* **376**, 37–43 (1995).
2. Tewari, M. *et al. Cell* **81**, 801–809 (1995).
3. Ray, C. A. *et al. Cell* **69**, 597–604 (1992).
4. Miura, M., Zhu, H., Rotello, R., Hartwieg, E. A. & Yuan, J. *Cell* **75**, 653–660 (1993).
5. Kuida, K. *et al. Science* **267**, 2000–2003 (1995).
6. Gagliardini, V. *et al. Science* **263**, 826–828 (1994).
7. Boudreau, N., Sympson, C. J., Werb, Z. & Bissell, M. J. *Science* **267**, 891–893 (1995).
8. Li, P. *et al. Cell* **80**, 401–411 (1995).
9. Lazebnik, Y., Cole, S., Cooke, C., Nelson, W. & Earnshaw, W. *J. Cell Biol.* **123**, 7–22 (1993).
10. Wang, Z. Q. *et al. Genes Dev.* **9**, 509–520 (1995).
11. Fernandes-Alnemri, T., Litwack, G. & Alnemri, E. S. *J. biol. Chem.* **269**, 30761–30764 (1994).
12. Wang, L., Miura, M., Bergeron. L., Zhu, H. & Yuan, J. *Cell* **78**, 739–750 (1994).
13. Kumar, S., Kinoshita, M., Noda, M., Copeland, N. & Jenkins, N. *Genes Dev.* **8**, 1613–1626 (1994).

ECONOMICS

Scales and stock markets

Allan Timmermann

DESPITE more than 30 years of research, no single characterization of the distribution of stock returns is widely accepted in economics. In their paper on page 46 of this issue[1], Mantegna and Stanley propose a new and potentially powerful approach to model the finding that the distribution of high-frequency stock returns is highly peaked in the centre and has tails that are too 'fat' to be consistent with standard distributional assumptions.

Their idea is appealingly simple: use separate functions to model the centre and the wings of the distribution of returns on the Standard & Poor's 500 index. More specifically, Mantegna and Stanley suggest applying a Lévy stable distribution to the centre of the distribution and then adding exponentially declining tails. Stable distributions have the important property of additivity: if X and Y are drawn from a stable distribution, this will also hold for their sum. This is a convenient property for most economic data which are the result of time aggregation. Furthermore, the second moment of the Lévy stable distribution will only be finite for certain parameter values[2].

Exponential decline of the tails guarantees that the variance of the distribution of stock returns is finite. Because one can never decide from a finite sample of observations whether the data are generated from a distribution with finite or infinite variance, the exponentially declining tails are best interpreted as an assumption based on empirical observations. Finite sample estimation of the tails of a distribution is complicated by the relatively small number of tail observations. So it is logical to attempt separately to model the centre of the return distribution, for instance by truncating the largest observations from the sample. Further research is needed to establish the point at which the centre distribution ceases to apply and the wing distribution takes over. Mantegna and Stanley suggest an 'eye-balling' procedure based on their Fig. 2 (page 48), but alternative estimation-based procedures might also be a possibility.

Proper modelling of the distribution of stock returns is important because of its significance for investors' management of risk. Standard financial models assume that investors are risk averse. Just how much risk an investor takes on by holding, say, the market index modelled by Mantegna and Stanley, is reflected by the distribution of those returns. Hence if an investor, wrongly, assumes that returns are drawn from a normal distribution, the risk taken on by holding the Standard & Poor's 500 index is likely to be much higher than expected.

The shorter the observation interval, the more do financial-returns data tend to deviate from the benchmark normal distribution: intra-day data is typically found to have a leptokurtic ('fat-tailed') distribution, whereas over longer periods, such as a quarter or a year, the leptokurtosis largely disappears. This information on the time-aggregation properties of stock returns is often ignored as researchers concentrate on deriving models for a specific period of time. In contrast, in their paper Mantegna and Stanley cleverly exploit the scaling properties implied by the Lévy stable distribution to estimate the parameters of the distribution of stock returns. Judged by their Fig. 1*c* (page 47), this scaling seems to be quite effective at least for the central part of the distribution.

The leptokurtosis observed in the returns of many financial indices is not necessarily best modelled as the outcome of draws from a single distribution. First, it is possible that returns could be generated by a mixture of distributions[3,4]. Discrete mixtures of normal or Student's *t*-distributions can generate fat tails while maintaining a relatively small value of the standard deviation of the resulting distribution. The mixing may also vary over time, as in the case of subordinated stochastic processes[5], and reflect the difference between clock time and activity time, taking variations in trading volume as the proxy.

Non-stationarities[6] or time-varying conditional moments[7] of the process generating the returns data are other possibilities. Volatility of stock returns tends to cluster in time[8], periods of highly variable stock prices being more likely to follow if prices previously were volatile than if they were calm. The large literature on ARCH processes documents this persistence in the volatility of returns and these models can generate fatter tails in the distribution of stock returns compared to the normal distribution. (ARCH, or autoregressive conditional heteroskedasticity models, allow the second conditional moment (variance) of a time series to be a function of the history of past realiza-

1. Mantegna, R. N. & Stanley, H. E. *Nature* **376**, 46–49 (1995).
2. Mandelbrot, B. *J. Business* **36**, 394–419 (1963).
3. Granger, C. W. & Orr, D. *J. Am. statist. Ass.* **67**, 275–285 (1972).
4. Kon, S. J. *J. Finance* **39**, 147–165 (1984).
5. Clark, P. K. *Econometrica* **41**, 135–155 (1973).
6. Pesaran, M. H. & Timmermann, A. *J. Finance* (in the press).
7. Loretan, M. & Phillips, P. C. B. *J. emp. Finance* **1**, 211–248 (1994).
8. Engle, R. F. *Econometrica* **50**, 987–1007 (1982).
9. Hamilton, J. D. *Econometrica* **57**, 357–384 (1989).
10. Hamilton, J. D. & Susmel, R. *J. Econometrics* **64**, 307–333 (1994).

tions of the process. GARCH, or generalized ARCH models, provide a more flexible way of accounting for the persistence often observed in squared stock returns.) Interestingly, Mantegna and Stanley report that the scaling property of stock returns in the sample is not well approximated by a GARCH(1,1) model. It is possible that this would not be so if a more elaborate ARCH model were used, but their result is consistent with frequent findings that ARCH models cannot fully account for the leptokurtosis observed in high-frequency financial returns.

Changes in institutions or in the economic regime may also account, at least partially, for the observed leptokurtosis in the distribution of stock returns. Because this view allows for the possibility that large outliers in the tail of the distribution of stock returns are drawn from a different distribution than the observations in the centre, it falls well in line with the approach suggested by Mantegna and Stanley. No study so far has been able to explain the events during the market 'meltdown' of 19 October 1987 as a 'reasonable' draw from a distribution that also describes the price dynamics during more normal times. A class of Markov switching models[9] allows for time-dependence in the mixing of distributions of stock returns corresponding to different regimes. For common stock indexes there seem to be at least two regimes, one with high variance and low (negative) mean returns, and another with low variance and positive mean returns. These models can be combined with ARCH processes to provide a possibly better fit of the distribution of returns[10].

In view of the strong evidence of time-varying parameters of the distribution characterizing high-frequency stock returns, the scaling approach proposed by Mantegna and Stanley should not be regarded as a substitute for existing models such as ARCH or regime switching. Instead it is likely that the two approaches can be fruitfully combined by using the distribution suggested by Mantegna and Stanley to model the residuals from one of the classes of models which has proved successful in forecasting the volatility of stock returns. □

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OBITUARY

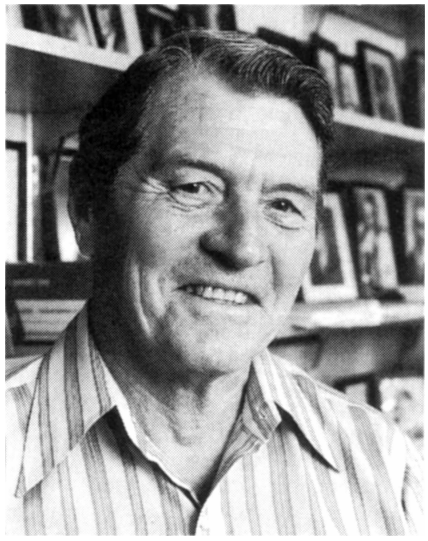
Christian B. Anfinsen (1916–95)

CHRIS Anfinsen died suddenly on 14 May at the age of 79. He was the quintessential protein chemist, acutely aware of both the chemical and biological sides of the field. In 1972, while he was chief of the laboratory of chemical biology at the National Institutes of Health, he shared the Nobel prize in chemistry with Stanford Moore and William Stein, awarded for pioneering work relating the structure and function of the enzyme ribonuclease. At the time of his death he was professor of biophysical chemistry at Johns Hopkins University in Baltimore.

In the late 1940s, before even the structure of DNA was known, Anfinsen began an experimental study of protein biosynthesis. The incredible complexity of this process was then only just becoming evident, but the general outline and basic requirements were eventually laid out in his seminal book *The Molecular Basis of Evolution* in 1959. His careful thinking in this uncharted area was to serve him well.

The appearance in the mid-1950s of a large sample of the bovine enzyme pancreatic ribonuclease, provided with some foresight by the Armour Company, enabled him to diversify his activities in a more chemical direction. Although he worked on aspects of the amino-acid sequence of the ribonuclease chain, the sequence itself was largely solved by Stein and Moore at the Rockefeller Institute: it was only the second complete sequence to be determined. Chris and his team focused on the effects on the enzyme's structure and catalytic properties of covalently modifying the peptide chain by proteolytic cleavage and by chemical means. The possibility for modifying a specific sequence genetically was of course still decades away.

One modification he was trying to achieve was to reduce the four disulphide bonds in the native molecule to eight sulphydryl groups. No method could be found by which this reaction could be carried to completion without the use of a denaturing solvent such as 8 M urea to open up the molecule and



make the S–S groups accessible to the reducing agent. This process resulted in the complete loss of the enzyme's catalytic activity, but it was not clear whether this was due to the denaturing conditions, which was to be expected, or whether the conversion of the four S–S groups to eight SH groups might itself be enough to remove the activity.

To prepare a linear chain for sequencing, Stein and Moore also needed to cleave the disulphide groups, and chose oxidation to yield eight sulphonic acid functions; this reaction is irreversible, so all catalytic activity was lost. To no-one's surprise, the product in aqueous solution showed no evidence of any residual structure apart from a random coil.

In contrast to sulphonic acid groups, sulphydryl groups can readily be reoxidized to the disulphide form. Anfinsen dialysed away the urea from his reduced sample in an oxygen-free atmosphere: nothing seemed to happen. The solution was then left in a beaker open to the air. Overnight, a large amount of the original catalytic activity of the enzyme was restored — the protein had reformed its native structure, unaided! The enormous implications of this seemingly simple experiment were immediately obvious to Anfinsen: all the information necessary to convert the randomly coiled peptide chain into its unique, biologically active structure was contained in the sequence of amino-acid residues in the chain. Herein lay the answer to the last step in protein biosynthesis — straight chemistry, no biological 'magic'.

Confirmed in later years by dozens of papers from his own laboratory and thousands from others, this statement is the central dogma of what is now termed the 'protein-folding problem'. A detailed understanding of this eludes us even now, but the central fact still stands. The fascinating recent work on chaperonins has generated a whole new level of complexity, but the information transfer from gene to native structure remains dependent only on the sequence. A much longer review would be required to cover all of Chris Anfinsen's contributions to the chemistry and biology of proteins, but he will retain his major place in the history of science because of a simple experiment involving a beaker and a prepared mind. Frederic M. Richards

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