two strains, the amplified size class remained the same; in the third strain, however, one expansion produced a single prominent extrachromosomal *inter-Alu* band while the second expansion produced three size classes. This suggests that the different sizes of extrachromosomal circles appearing in different cell strains may be due to stochastic events in culture rather than donor genotype alone.

Another hypothesis would be that circular species containing *inter-Alu* sequences arise via homologous recombination[24] or gene conversion[23] between genomic *inter-Alu* copies and endogenous circular species, and are subsequently amplified during ageing *in vitro* or *in vivo*. A further possibility, that such circular forms are infectious and transmitted to cells or individuals in a time-dependent fashion, may be unlikely in view of the different circular sizes appearing in several late-passage fibroblast cultures grown concurrently. That is, the chance of infection in all four cultures, each with different viral species, seems remote. In this context it is also noteworthy that none of the aged lymphocyte donors had previous contact with members of our laboratory.

Analogy of the *inter-Alu/Alu* cluster to prokaryote and eukaryote transposable elements

Alu repeat units in human DNA possess many properties characteristic of prokaryotic and eukaryotic insertion sequences[25-28]: most units are flanked by short direct repeats; they contain promoter sequences for an RNA polymerase (pol III); they are found both in circular DNA molecules[5,16] and scattered within the genome; and they have evidently inserted into other genomic sequences, forming flanking direct repeats by duplication of a segment of the pre-insertion site sequence[29].

The *inter-Alu* sequence together with adjacent *Alu* repeat units is structurally analogous to several prokaryote transposons, which consist of two identical insertion sequences flanking a central region that generally encodes known gene products[25]. Several transposable elements which have been characterized in eukaryotes share this 'transposon-like' structure: for example, Ty*1* in yeast, and *copia*, *412* and *297* in *Drosophila*[25,26]. Although the case for transposability of *Alu* itself is reasonably strong[27-29], it must be emphasized that transposition of the *inter-Alu* sequence remains to be demonstrated.

Thus, although many aspects of the polymorphic *inter-Alu* sequence have yet to be resolved, their striking association with both *in vitro* and *in vivo* ageing poses an intriguing problem. Regardless of whether they are implicated as causative agents in senescent loss of adaptive function, or instead prove to be a secondary phenomenon perhaps reflecting the more general loss of genomic stability during the lifespan, they reveal a remarkable potential for structural flux in eukaryotic genomes.

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LETTERS TO NATURE

Inflation and time asymmetry in the Universe

P. C. W. Davies

Department of Theoretical Physics, The University,
Newcastle upon Tyne NE1 7RU, UK

The recently proposed inflationary Universe scenario[1-4] explains several of the mysteries of modern cosmology. I argue here that it also provides a natural explanation for the origin of time asymmetry ('time's arrow') in the Universe. The new feature which inflation injects into this long-standing problem is the temporary dominance of the cosmological term in the gravitational field equations, which acts as a sort of repulsive gravity. This term generates huge quantities of energy and radiation (or matter) entropy, while drastically reducing the entropy density of the gravitational field. It thus establishes a large gap between the radiation entropy and the gravitational entropy, which gravity is now trying to close.

Most discussions of the origin of 'time's arrow' appeal ultimately to cosmology[5]. There is a paradox that, according to the standard hot big-bang model, the material contents of the Universe began in a condition of thermodynamic equilibrium (primeval chaos), whereas the Universe today is highly ordered, and far from equilibrium. The apparent reduction in entropy implied seems to conflict with the requirement of the second law of thermodynamics, which demands that entropy should never decrease. The natural tendency is for the Universe to 'run down' towards the heat death, and the problem is to explain how it was 'wound up' in the first place.

The paradox is partially resolved once it is appreciated that the Universe is an open system, whereas the second law applies to closed systems. The openness involved is not, however, of a spatial nature. The crucial observation is that the local cosmological material is open to the external cosmological gravitational field, through which, by the general theory of relativity, one describes the expansion of the Universe.

Specifically, in the high-density primaeval phase (in a simplified, conventional model) the expansion, although rapid, was much slower than the relaxation rate for typical particle processes in the cosmological material. The structure of the material therefore easily adjusted itself to the evolving circumstances, such as declining temperature, without lagging behind equilibrium conditions. Entropy was at a maximum consistent with the cosmological constraints.

After a few seconds, however, the situation changed dramatically as nucleosynthesis became entropically favoured, because the relaxation time for nuclear burning was very much longer than the expansion time scale of that epoch. The material thus got out of step with the expansion, and an entropy gap opened up. There was simply insufficient time for equilibrium to be established. Most of the material remained 'frozen' in the form of low-entropy hydrogen, which is now synthesizing heavy elements in stars in an attempt to restore equilibrium. Our present existence is due to the lag induced by the rapid cosmological expansion in the first few minutes which had the effect of 'winding up' the Universe. Rather than the entropy decreasing, what has happened is that entropy has actually increased, but the maximum possible entropy also increased—and faster—due to the changing cosmological constraints implied by the expansion of the Universe. This gap-opening mechanism has been made explicit in a recent model calculation[6].

Invoking the expansion of the Universe provokes us to contemplate the entropic qualities of the cosmological gravitational field in particular, and gravity in general. The idea that there should be a 'gravitational entropy' has been much discussed[5,7–9], while Bekenstein[10] and Hawking[11] supplied an expression for the entropy of a black hole.

Although we still lack a formulation for the entropy of an arbitrary gravitational field, some qualitative features of gravitational entropy are easily deduced. The tendency of self-gravitating systems to grow clumpy and inhomogeneous from smooth initial states is obviously irreversible, the black hole representing the equilibrium end state of this spacetime crumpling. This time-asymmetric tendency ought to receive expression within a generalized second law of thermodynamics[7].

Accepting that a smooth gravitational field represents a low-entropy state, one arrives at a curious reversal of the foregoing conclusion pertaining to the cosmological material. Whereas the material could have started out in thermodynamic equilibrium, and thus did not need to be created in any very special state to account for the currently observed order in the Universe, the gravitational field apparently started out in an exceedingly improbable state. The exceptional uniformity of the Universe on the large scale testifies to the relatively smooth nature of the gravitational field in the primaeval phase.

This paradox has been emphasized by Penrose[8], who poses the problem in the following way. If, instead of being distributed more or less evenly across the cosmos, the cosmological material were accumulated into a black hole, the entropy of the hole (using Hawking's formula[11]) would be some 10^{30} times greater than the actually observed entropy of the Universe. Assuming the usual relationship between entropy and statistics, this gives odds of $\sim 10^{10^{30}}$ to one against the present gravitational arrangement happening by chance. Why, asks Penrose, when there are so many ways for the big bang to cough out black holes, did it actually disgorge smoothly distributed matter? How did the Universe manage to go bang in such an improbable way?

The argument applies not only to black holes, but also to the general isotropy and homogeneity of the Universe. With so many degrees of freedom available for expansion, why was all the explosive energy concentrated in a single dilatory mode of uniform distension? A highly turbulent, irregular Universe would have been much closer to thermodynamic equilibrium and therefore, on *a priori* grounds, far more probable[12].

These considerations receive an entirely new twist in the light of the so-called inflationary Universe scenario. The essential idea is that at around 10^{-35} s the Universe was in a hot phase in which the grand unified force had not yet differentiated into its nuclear and electromagnetic components. Once the temperature had dropped below the GUTs value of around 10^{30} K, the way lay open for a 'freeze out' to occur through a phase transition. One consequence of this transition is an enormous jump in the value of the cosmological constant, Λ. Being essentially zero today, this constant must have been colossal in the early Universe and, driven by the associated repulsion, the Universe would have embarked on a period of exponential expansion with a GUTs e-folding time.

Given long enough, the inflationary phase would be capable of smoothing out any initial anisotropy and inhomogeneity by 'stretching the bumps'. At the end of inflation, as pointed out by Guth[1], the Universe would be close to the uniform structure we observe today.

We are thus led to the following scenario. In the beginning, quantum gravity dominated. At the end of the Planck era (10^{-43} s) spacetime was irregular on all scales (see, for example, fractal spacetime in ref. 7), in the form of thermal spacetime 'foam', representing maximum entropy. The Universe therefore began in an arbitrary, rather than remarkably specific, state. This is precisely what one would expect if the Universe is to be explained as a spontaneous random quantum fluctuation from nothing. Because the GUTs time is not much longer than the Planck time, the quasi-classical post-planckian era would have been too short for significant black hole formation to have occurred before inflation set in, and any holes so formed would have been microscopic and would therefore have rapidly evaporated.

Inflation began when the thermal energy from the Planck foam was redshifted below the false GUTs vacuum energy by the expansion. At this point the crucial mechanism for the gravitational winding of the Universe was set in motion. The aforementioned tendency of the gravitational field to grow clumpy with time only applies so long as the cosmological term is negligible. If the cosmological repulsion dominates, the tendency for spacetime to crumple is reversed. Instead it becomes unstable against exponential growth with asymptotic approach to (smooth and maximally symmetric) de Sitter space. de Sitter space represents the equilibrium end state (maximum entropy state) of a spacetime with a non-zero Λ.

There is thus a close parallel between the collapse of matter to form a black hole, which wipes out most of the information about the initial state (the 'no-hair' property) and the inflationary Universe, which wipes out the details of the initial cosmological phase. Both can be regarded as efficient entropy-generating (information-destroying) processes. A de Sitter 'no-hair' theorem has been conjectured by Hawking and Moss[13]. Supporting evidence for this conjecture comes from the work of Frieman and Will[14] and Barrow[15].

This curious two-edged instability of gravity in the presence of a cosmological constant has been known since the early analysis of the Einstein Universe. This static model is doubly unstable against collapse or exponential expansion. Note that if the initially static Universe has radius R, then according to the Einstein equations

$$R \sim GM \tag{1}$$

where M is the total mass. Equilibrium (unstable) requires

$$\Lambda \sim GM/R^3 \tag{2}$$

We may now compare the entropy of the inflationary fate with that of collapse by comparing the area of the de Sitter horizon (taken to be the gravitational entropy of de Sitter space[16]) with that of an equivalent-mass black hole. From equations (1) and (2) the former ($\sim\Lambda^{-1}$) is clearly $\simeq$ the latter ($\sim G^2M^2$).

So long as Λ persists, it remains entropically favourable for the Universe to continue inflating and decrinkling. However, exponentiation drops the temperature rapidly to nearly zero, and the false quantum vacuum becomes unstable against a transition to the true vacuum. Whether this takes place by supercooling and quantum tunnelling, or slow decay, is irrelevant here. What matters is that once Λ vanishes, the entropic situation is abruptly transformed again. It becomes favourable once more for the Universe to grow clumpy. Suddenly it is in a state of much-less-than-maximum entropy.

In compensation there is a huge and sudden increase in the matter entropy as the change of quantum state from an essentially zero-entropy vacuum state to a high temperature thermal state takes place. This thermal release has been called the 'grand bang' by Linde[17] and is a classic example of entropy generation caused by a lag behind equilibrium conditions. The quantum state, either because of supercooling or sluggishness, hangs in the 'wrong' state for many inflationary e-folding times. During this phase the famous 'gap' opens up between the maximum possible and actual entropies of the quantum field. When it stops, a huge quantity of entropy is dumped into the matter fields. This grand-bang entropic leap is irreversible. A recontracting Universe arriving at the big crunch would not undergo 'deflation', for this would require an exceedingly improbable conspiracy of quantum coherence to reverse-tunnel through the phase transition. There is thus a distinct and fundamental asymmetry between the beginning and end of a recontracting Universe caused by the specific interplay between the quantum state and gravitational behaviour of the high temperature Universe.

Natural though this inflationary explanation of time asymmetry may be, we still seem to be left with a paradox. Although we can trace dynamically how the Universe can start out in thermodynamic equilibrium at the Planck era, but still achieve its present relatively smooth gravitational condition and less-than-maximum matter entropy, the total system of matter and gravitational field ought to be closed. There is then a thermodynamic puzzle as to how a closed system can progress from a maximum entropy to less than maximum entropy. Whereas the changing cosmological gravitational field can drive an entropy gap for the matter by acting as a changing constraint, what constraints change for the total system?

The resolution of this paradox comes from a careful consideration of the nature of energy in a cosmological context. To say that entropy is a maximum means 'a maximum for the given energy'. If the energy goes up, the entropy can go up too. Thus, a box of thermal radiation will have maximum entropy, but if more energy is introduced into the box (that is the temperature is raised) the entropy will rise. Now in cosmology, energy is not conserved. This is illustrated dramatically by the inflationary Universe scenario, where the cosmological constant acts like a fluid with a negative pressure. Thus, as the Universe expands, negative work is done, and the Λ energy in a co-moving volume rises. In fact, Λ acts such that the energy density remains constant in spite of the expansion. At the end of the inflationary phase this huge additional energy is thermalized and dumped into the matter (matter includes radiation) fields. This is the energy which provides Guth's so-called 'free lunch'[18]. Thus, the matter entropy, which was a maximum at the Planck era (Planck temperature at the Planck time) is now enormously greater than it would have been after inflation, had not the Λ energy thermalized.

This huge increase in matter entropy could more than offset any decrease in gravitational entropy. In the absence of a proper theory of gravitational entropy we cannot say, however, whether the inflationary stretching of the irregularities left the gravitational entropy in a co-moving volume unchanged, or actually lowered it. Nevertheless, the gravitational entropy density fell rapidly as the inflation generated more and more space.

The effect of inflation, then, was vastly to enhance the ratio of matter entropy to gravitational entropy, which at the Planck time was probably of the order of unity. We therefore have an explanation for why the gravitational entropy of the Universe is so low. The huge imbalance between the observed entropy of matter and radiation, and the gravitational entropy the Universe would have, had all this energy collapsed into a black hole, arose because the Λ energy was converted to matter entropy and not gravitational entropy at the end of the inflationary era. Since then, gravity has been trying to redress the balance. We thus have a vast reservoir of relatively negative gravitational entropy.

In conclusion, it is now possible, using the inflationary scenario, to postulate a Universe which begins in an arbitrary, equilibrium state, both as far as matter and gravity are concerned but which, because of the linkage between the quantum state of the matter and the gravitational behaviour through Λ, first gets wound up gravitationally by inflation, then gets wound up in the nuclear sense at a much later epoch by the conventional expansion. The remaining history of the Universe is the subsequent attempt to unwind by gravitational clumping (galaxies → stars → blackholes → superholes) and nucleosynthesis (hydrogen → helium → iron). Together, these two evolutionary chains account for all the observed macroscopic time asymmetry in the physical world and imprint on our environment a distinct arrow of time.

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Optical variability of QSOs and gravitational lenses in galactic haloes

Roland Bacon* & Jean-Luc Nieto†

Observatoires du Pic-du-Midi et de Toulouse, Laboratoire Associé au CNRS No. 285, 65200 Bagnères-de-Bigorre, France

The problem of QSO–galaxy associations has been analysed[1,2] by taking into account different classes of QSOs with the conclusions that: (1) the strong excess of 3C QSOs near bright galaxies[3] is not confirmed by larger QSO samples, which do not show any tendency towards QSO–galaxy associations, so that the 3C QSOs appeared as a statistical fluctuation[1]. (2) Amongst various classes of QSOs, optically variable (OV) QSOs from a list of 41 objects[4] showed a significant excess of QSOs near galaxies[2]. But to be considered as a physical effect this excess needed confirmation from a larger sample of QSOs. Canizares[5] has used the possibility of gravitational lens effects on QSOs caused by stars in galactic haloes to explain the presence of numerous QSOs near bright galaxies[6], whose statistical significance is quite controversial (see refs 7–11). Canizares attributed to such QSOs one physical characteristic—their optical variability caused by the relative motions of the Earth and of the star acting as a gravitational lens. As these theoretical considerations gave a new insight on our previous statistical study, we decided to consider a larger sample of OV QSOs. We now present this new analysis and discuss the results in the light of Canizares' considerations.

We followed the same procedure as in ref. 2. The galaxies were taken from the Zwicky catalogues ($m \leq 15.7$ and $\delta > -3°30'$). The QSOs came from the list set up by Nieto and Seldner[12] made up of QSOs having an accurate position and a redshift determined with some confidence provided $z > 0.1$.

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* Present address: Observatoire de Lyon, 69230 Saint-Genis-Laval, France.

† To whom correspondence should be addressed.