sory neurons that receive more than one type of sensory signal have been found in different areas of human and monkey brains, for example, in the parietal areas (vision, hearing, and touch) and in the superior colliculus (vision and hearing) (*7*). This has led to the popular notion that cross-modal connections simply reflect the existence of multisensory neurons. Macaluso *et al.* go beyond this explanation, proposing that cross-modal effects are the result of signals—carried by multisensory neurons projecting from the parietal areas of the somatosensory cortex back to the primary visual cortex—that modulate the activity of visual neurons. Their proposal is similar to that put forward to explain the modulation of auditory cortical activity by visual signals from moving lips (*8*) or from facial expressions (*4*) during speech perception.

It is unlikely that multisensory neurons by themselves could account for all cross-modal effects without some feedback from the visual (or in some cases the auditory) cortex. In the sensory cortical architecture proposed by Macaluso *et al.*, multisensory neurons and their back-projections each have their own distinct functions. Multisensory neurons—or structures that establish connections between different sensory signals, such as the amygdala (*9*)—alert the organism to possible coincidences among sensory stimuli (by detecting similarities among the when, where, what, and why for each stimulus) and so behave as possible event detectors (see the figure). Presumably, simultaneous administration of visual and tactile stimuli to human volunteers by Macaluso *et al.* was crucial to their finding that the lingual gyrus was activated by the integration of both sensory signals. If the two stimuli had been administered at slightly different times, it is possible that activation of the lingual gyrus would not have been observed. Also, the human volunteers were only shown very simple objects. It would be interesting to know whether more complex visual stimuli would have resulted in lingual gyrus activation. Synchrony between visual and auditory stimuli (*4*, *8*, *10*) as well as object identity (moving lips, facial expressions) is crucial for the cross-modal integration of different sensory signals.

At last, we are beginning to understand how the brain detects only the biologically important combinations of sensory stimuli that emanate from our complex world.

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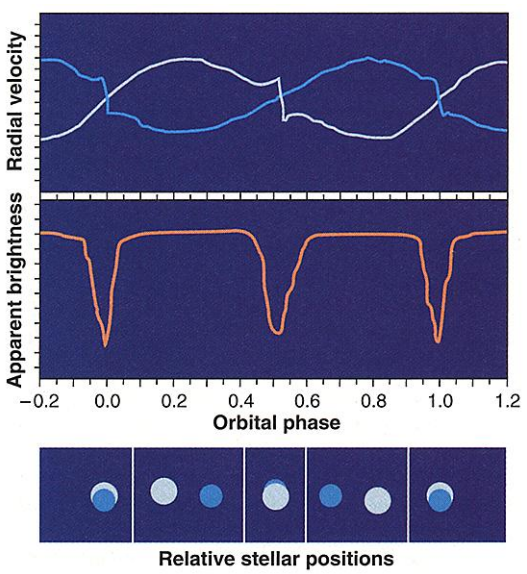
PERSPECTIVES: ASTRONOMY

The Distance to the Large Magellanic Cloud

Andrew A. Cole

After nearly a century of argument, astronomers may soon be able to agree on the distance to the most important cosmic milepost, the Large Magellanic Cloud (LMC). This larger of two nearby galaxies is gravitationally bound to the Milky Way and visible to observers in the Southern Hemisphere.

The LMC gained its cosmological importance because it is a convenient benchmark for extragalactic distances; nearly all extragalactic distances measured to date are only known relative to the distance from Earth to the LMC. Despite its importance in observational cosmology, however, the distance to the LMC (d_{lmc}) remains uncertain to within roughly ±10%. This uncertainty in d_{lmc} propagates directly into an uncertainty in the expansion rate of the universe, which in turn confounds attempts to reconstruct the history and predict the fate of the universe. The confusion over d_{lmc} is the single largest source of error for the recently completed Hubble Space Telescope (HST) Key Project on the Extragalactic Distance Scale, whose goal was to determine the Hubble constant to within 10%. A mean value of d_{lmc} = 50 kiloparsecs (1 kpc = 3260 light years = 3.09×10^{16} km) was adopted in the project, but the relevance of this value remains a matter of dispute (*1*).



Toward an accurate estimate of cosmological distance. The radial velocity and light curves of an eclipsing binary star system allow the determination of their relative masses and radii; spectroscopy allows determination of their temperatures. The absolute distance from Earth then follows from a simple formula.

The true value of d_{lmc} has remained enigmatic because measurements show no tendency to cluster about a well-defined mean value but rather show a broad scatter with an apparently bimodal shape. This shows that systematic errors resulting from experimental bias are dominant over random uncertainties in the measurement. The value of d_{lmc} can be derived with a multiplicity of techniques, most of which are relative to local calibration objects and each of which is susceptible to different sources of error. As a result, some authors derive distances up to 20% shorter than others using nearly identical methods. Most published estimates of d_{lmc} cluster around "short" values, near 46 kpc, or "long" values, near 54 kpc (*2*).

For the vast majority of stars, the only direct distance measurements are made with trigonometric parallax. This method measures the apparent displacement of a star relative to a background field of much more distant objects (such as quasars) as Earth moves in its orbit around the sun. Modern charge-coupled device detectors have pushed the limit of parallactic distances to a few hundred parsecs, orders of magnitude smaller than d_{lmc}. Therefore, a system of "standard candles" for the determination of relative distances had to be developed.

One of the best studied standard candles is a class of variable stars known as Cepheids. The pulsation period of a Cepheid variable is

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tightly correlated with its luminosity, and the distance to a Cepheid of known period can thus be readily determined from its apparent brightness (*3*). The Cepheid period-luminosity relation was first discovered in surveys of the Magellanic Clouds, which contain over a thousand known Cepheids (*4*). Using the Cepheids of the LMC, an accurate relative distance scale was quickly established (*5*). The Key Project has extended the Cepheid-based relative distance scale out to the nearest large clusters of galaxies, in Virgo and Fornax, 300 to 400 times as distant as the LMC. However, the absolute calibration of the Cepheid-based distance scale requires independent distance estimates for a large sample of local Cepheids in order to set the zero point of the period-luminosity relation. Unfortunately, Cepheids are intrinsically rare in the solar neighborhood, and none exist within 100 parsecs of the sun. The distance scale zero point therefore has to be estimated indirectly, contributing to the controversy over d_{lmc}.

The European Space Agency's Hipparcos satellite vastly extended the sample of stars for which accurate distances are known beyond ground-based studies. Hipparcos provided high-quality parallaxes for more than two dozen Cepheid variables (*6*). However, the discrepancy between the long and short d_{lmc} was not mitigated. This is because the number of Cepheids with high-quality parallaxes is still so small that statistical biases in sample selection play a dominant role in the determination of the distance scale zero point.

A promising method for the direct determination of d_{lmc} uses eclipsing binary stars. These stellar systems comprise two stars in mutual orbit, whose relative positions yield a regular pattern of variability as each star occults the other in turn. The method is conceptually simple but has only recently become feasible because it requires ultraviolet spectrophotometry and accurate theoretical models of stellar atmospheres. Observations at multiple orbital phases yield an accurate determination of the absolute luminosity of the binary and hence a distance that is independent of local calibrators (see the figure). Early results, based on just one binary, favor a distance of 46 to 48 kpc for the LMC, near the mean of other recent determinations and ≈6% shorter than the value adopted by the HST Key Project (*7*).

During the next decade, a new generation of proposed satellite missions promise to greatly reduce the errors in d_{lmc}. Two planned NASA missions are the Full-Sky Astrometric Mapping Explorer (FAME, launch date 2004) and the Space Interferometry Mission (SIM, launch date 2006) (*8*). FAME will be a survey mission that will extend the work of Hipparcos by increasing the number of reliable Cepheid parallax measurements by an order of magnitude. SIM will be the first astronomical satellite to use optical interferometry. This technological innovation is expected to enable parallax measurements of Cepheids in the LMC for the first time. By eliminating all intermediate steps, it may finally be possible to directly determine the distance to the LMC and, by extension, to the rest of the galaxies in the universe.

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PERSPECTIVES: APOPTOSIS

Mitochondria—the Death Signal Integrators

Catherine Brenner and Guido Kroemer

The mitochondrion, the cell's Pandora's box, contains potentially harmful proteins that it keeps hidden away. Activation of these harmful proteins sets in motion programmed cell death (apoptosis) pathways that result in the demise of the cell. In many of these pathways, permeabilization of mitochondrial membranes is a critical event that results in release (from the mitochondrial intermembrane space) of various molecules that are crucial for apoptosis. Such molecules include enzymes called procaspases, cytochrome c (a caspase activator), Smac/Diablo (a caspase coactivator) (*1*), and an apoptosis-inducing factor, which activates the nucleases that chop up DNA into small fragments. Now, on page 1159 of this issue, Li and colleagues (*2*) report the tantalizing discovery that a potential proapoptotic transcription factor, TR3 (also called Nur77 or NGFIB), normally present in the nucleus, can move to mitochondria where it triggers membrane permeabilization and apoptotic cell death.

Like other proteins in the steroid/thyroid receptor superfamily, TR3 is a transcription factor with a central zinc finger DNA binding domain flanked by transactivation domains. In contrast to other steroid receptors, however, the endogenous ligand of TR3 (which is predicted to interact with the carboxyl-terminal half of the receptor) has not yet been identified, making TR3 an "orphan" receptor. TR3 forms homodimers with itself and heterodimers with other proteins from the same family, in particular with the 9-*cis*-retinoic acid receptor (RXR). The TR3 DNA binding domain interacts with a specific DNA octamer sequence, the Nur77/NGFIB-binding response element (NBRE), and, when in a heterodimer with RXR, also with the retinoic acid response element. Usually, TR3 (and RXR) are imported into the nucleus after their synthesis in the cytoplasm. This implies that most if not all of TR3's activity is in the nucleus. Under specific circumstances, however, TR3 can be exported back to the cytoplasm. This halts its transcriptional activity (*2*) and may also suppress that of RXR, which accompanies TR3 back to the cytoplasm (*3*).

Surprisingly, as Li *et al.* show, TR3 may also induce mitochondrial membrane permeabilization. Indeed, in cells undergoing apoptosis, TR3 (fused to a green fluorescent protein marker) specifically translocates to mitochondrial membranes, as revealed by its punctate staining pattern in the cytoplasm. Recombinant TR3 induces the release of cytochrome c when added to purified mitochondria in vitro (*2*), suggesting that TR3 permeabilizes mitochondrial membranes on its own, without the participation of additional proteins.

TR3 is overexpressed in response to certain apoptotic stimuli. For instance, TR3 is up-regulated by external stressors such as seizures or brain ischemia. Upon ligation of the T cell receptor by ligand, T cells switch on expression of the TR3

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