of neurons. Neurophysiologists have often found that the firing rate of each neuron in a population can be written as a smooth function of a small number of variables, such as the angular position of the eye (*4*) or direction of the head (*5*). This implies that the population activity is constrained to lie on a low-dimensional manifold.

What is the connection between such neural manifolds and the image manifolds we have just discussed? According to a well-known idea, memories are stored in brain dynamics as stable states, or dynamical attractors (*6*). Because the possible images of an object lie on a manifold, it has been hypothesized that a visual memory is stored as a manifold of stable states, or a continuous attractor (*7*). Recent studies of neural manifolds suggest that continuous attractors actually do exist in the brain (*8*, *9*). Whether they are the basis of visual and other types of perception remains to be resolved. If the answer is affirmative, then manifolds will prove to be crucial for understanding how perception arises from the dynamics of neural networks in the brain.

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PERSPECTIVES: MICROELECTRONICS

Flip the Chip

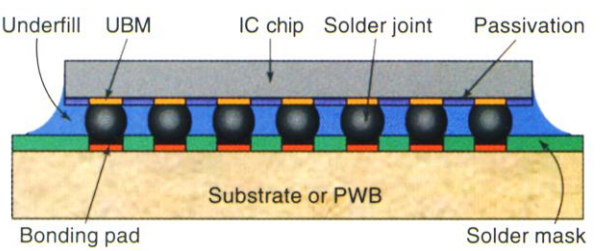
C. P. Wong, Shijian Luo, Zhuqing Zhang

Today's world is filled with fancy electronic products such as laptops, cellular phones, and digital cameras. In all of these systems, electronic packaging plays an important role by supplying power to chips, distributing signals between chips and among devices through interconnects, providing heat dissipation, and protecting components from environmental impact (*1*, *2*). As integrated circuit (IC) fabrication advances rapidly and the market for ever faster, lighter, smaller, yet less expensive electronic products accelerates, electronic packaging faces its own challenges. This is where flip chip packaging comes into play.

Conventional electronic packaging uses wire-bonding technology, in which the active side of the silicon chip faces up and interconnection is created by drawing gold, silver, or copper wires to the substrate. In contrast, in flip chip packaging, the active side of the silicon chip faces down and is directly connected to the substrate or printed wire board (PWB). This technology has many advantages over the conventional approach. It has a much higher input/output (I/O) count because the whole area underneath the chip can be used for interconnection. The shorter signal path between chip and board reduces inductance, thereby increasing signal propagation speed and greatly enhancing electrical performance. Because the chip faces down to the substrate, its backside can be used for heat dissipation. Finally, the entire interconnection on the chip can be made simultaneously in a single step, whereas in wire bonding only one wire is drawn at a time. Flip chip thus offers the possibility of low-cost electronic assembly for modern electronic products.

The authors are at the School of Materials Science and Engineering, Georgia Institute of Technology, Atlanta, GA 30332, USA. E-mail: cp.wong@mse.gatech.edu

Since the flip chip was first developed 40 years ago at Bell Labs, many variations of the design have been demonstrated. The most important form of flip chip is the solder bump interconnection or Controlled Collapse Chip Connection (C4) (*3*). In this method, solder bumps deposited on wettable metal terminals on the chip connect with matching bonding pads on the substrate (see the figure). The metal terminal (called under bump metal or UBM) consists of several layers that provide good adhesion to the chip and the solder bump and prevent oxidation of the metal terminal (*4*). Solder bumps can be fabricated through evaporation, electroplating, electroless plating, or screen printing. New technologies include solder jet printing and microball mounting.



Generic configuration of flip chip interconnection with underfill.

After the chip is placed on the substrate, the assembly is subjected to "solder reflow," a heating cycle that melts the solder bump. The surface tension of the molten solder prevents the chip from collapsing onto the substrate. One advantage of this process is that the chip can self-align as a result of the high surface tension of the molten solder. As long as enough solder touches the bonding pad on the substrate, perfect alignment can be achieved.

In the first generation of C4, ceramic substrates with a low coefficient of thermal expansion (CTE) matching that of the silicon were used. However, ceramic substrates are expensive and require high-temperature processing. Furthermore, their high dielectric constant aggravates the signal delay. Organic substrates are favorable because of their low dielectric constant and low cost, but high CTE differences between organic substrates and the silicon chip exert great thermal stress on the solder joints during temperature cycling. The larger the chip, the higher the stress and, hence, the shorter the solder joint fatigue life. This is why organic substrates could not be used in flip chips until underfill was invented in the late 1980s.

Underfill is a liquid encapsulate that is applied between the chip and the substrate. After conversion into a solid material during curing, it exhibits high modulus, high glass transition temperature, low moisture absorption, good adhesion toward chip and substrate, and low CTE matching that of the solder joint. Thermal stresses on the solder joints are redistributed among chip, solders, underfill, and substrate, thereby increasing the solder joint fatigue life 10 to 100 times (*5*).

With increasing application of flip chips on organic substrates, underfill technology becomes the key to achieving highly reliable packaging. However, current underfill materials have several drawbacks that limit their wide application. If an IC is assembled using flip chip without underfill, a failed chip can easily be removed from the substrate by melting the solder joint and replacing the failed chip by a new one. If underfill is applied, this rework process becomes very difficult because most currently used underfill materials are epoxy-based thermosets that go through an irreversible cross-linking (curing). Reworkable underfill materials may solve this problem. An acetal/ketal group has been incorporated into the epoxy resin so that the cured resin can be dissolved in acid and thus reworked (*6*). Epoxy resins containing thermally cleavable linkages

have also been used as reworkable underfills (*7*). Another approach is to use blowing agents that decompose at high temperature, giving off a large amount of gas. By blending the blowing agents into epoxy resins, underfills can be made reworkable (*8*).

Another drawback of conventional underfill is the long and tedious dispensing and curing process. A wafer level underfill material is in development to address this problem (*9*). Instead of dispensing the conventional underfill into the gap between the chip and the substrate after solder reflow, wafer level underfill can be applied directly onto the wafer. The wafer is then diced into individual chips for further assembly onto the substrate; final curing of underfill and solder joint connection occur simultaneously during solder reflow.

An approach that does not use underfill has also been pursued to enhance the reliability of flip chips on organic substrates. A polymer stress buffer layer is applied and flexible metal leads are built from the metal terminal on the chip (*10*). At the end of the leads, solder bumps are formed for flip chip interconnection. Through the deformation of the low-modulus buffer layer and the flexible leads, the thermal stress on the solder joints is released and the fatigue life of the solder joints is improved. The stress buffer layer, flexible leads, and solder bumps can all be fabricated on the wafer level. Because no underfill is used, the chip can be reworked easily.

Currently, only about 1% of all IC chips are assembled with flip chip technology, but given the rapid advances in microelectronics and electronic packaging, the application of flip chip technology is expected to increase dramatically in the near future. For small chips with low I/O counts, flip chips with stress buffer layers will play a major role, but for large chips with high I/O counts such as microprocessors, the stress buffer layer cannot ensure sufficient reliability. Wafer level reworkable underfill may enable low cost, high reliability flip chip assembly for these applications.

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PERSPECTIVES: NEUROBIOLOGY

A *Stargazer* Foretells the Way to the Synapse

Terunaga Nakagawa and Morgan Sheng

The chemical messenger glutamate moves from cell to cell, enabling excitatory neurons in the brain to communicate with each other. This neurotransmitter is released into the synapse by the presynaptic neuron, travels across the synapse, and then binds to glutamate receptors on the surface of the postsynaptic cell (see the figure). One class of glutamate receptor, the AMPA receptor, moves rapidly into and out of the postsynaptic membrane. The number of AMPA receptors in the postsynaptic membrane controls the strength of excitatory transmission between neurons and perhaps also the storage of memories in the brain. Consequently, there is much interest in elucidating how AMPA receptors make their way from their site of synthesis in the neuronal cytoplasm to distant postsynaptic membranes located at the end of neuronal processes called dendrites. Our current knowledge of this process is rudimentary, based largely on identification of the proteins that interact with the cytoplasmic carboxyl-terminal tails of AMPA receptor subunits (GluR) in the postsynaptic membrane. Chen *et al.* (*1*) report in yesterday's *Nature* that a transmembrane protein called stargazin (which is defective in the *stargazer* mutant mouse) is critical for bringing AMPA receptors to the cell surface and for targeting them specifically to postsynaptic sites. Their work reveals the unexpected involvement of stargazin in AMPA receptor trafficking, distinguishes two steps in the synaptic targeting of AMPA receptors, and suggests intriguing connections between AMPA receptors and calcium channels.

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The authors are in the Department of Neurobiology and Howard Hughes Medical Institute, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA. E-mail: sheng@helix.mgh.harvard.edu, nakagawa@helix.mgh.harvard.edu

The *stargazer* mutant mouse exhibits unusual head-tossing movements, an ataxic gait, and epileptic seizures. The epileptic phenotype has been attributed to hyperexcitability in cortical networks (*2*), and the ataxia to aberrant development of cerebellar granule neurons (*3*). The *stargazer* mutation disrupts the 38-kD stargazin protein, which has four predicted transmembrane domains and is homologous to the γ subunit of muscle voltage-gated calcium channels (*4*). In addition to its structural similarity to muscle calcium channels, stargazin alters the activity of a neuronal voltage-dependent calcium channel in vitro. Thus, stargazin may be the γ2 subunit of neuronal calcium channels, equivalent to the γ1 subunit of muscle calcium channels (*4*). The main cerebellar defect in *stargazer* mice is found in granule cells of the cerebellum, which display retarded differentiation (*3*) and almost complete loss of AMPA receptor synaptic responses (*1*, *5*), despite normal expression of AMPA receptor messenger RNA and protein. Yet, calcium channel activity seems relatively unaffected in these cells (*1*). In their new work, Chen *et al.* provide the connection between stargazin, AMPA receptor trafficking, and defective synaptic transmission in *stargazer* cerebellar granule cells (*1*).

Like other transmembrane receptors, AMPA receptors are presumably synthesized in the endoplasmic reticulum, processed in the Golgi apparatus, and transported to the cell surface in membrane vesicles (see the figure). In neurons, the problem is more complicated because AMPA receptors are transported to dendrites (rather than to axons) and ultimately become concentrated in a small patch of postsynaptic membrane (rather than being diffusely sprinkled across the surface of dendrites). How AMPA receptors make their way to the synapse is a key question. So far, we know only that the carboxyl-terminal tails of AMPA receptor subunits—which bind to proteins containing specialized protein interaction domains called PDZ domains—appear to be important for the localization or stabilization of AMPA receptors in the postsynaptic membrane (*6*–*9*).

With everyone investigating the interaction between AMPA receptor subunits and cytoplasmic proteins, no one expected that a transmembrane protein would be involved in AMPA receptor trafficking. But Chen *et al.* now report that cell surface expression and synaptic clustering of AMPA receptors is abolished in the cerebellar granule cells of *stargazer* mice, and that this mutant phenotype can be rescued by transfecting wild-type stargazin into these cells in vitro (*1*). Deleting the cytoplasmic carboxyl terminus of stargazin