capability of steel-frame buildings to resist severe shaking has not yet been fully explored.

Still, he and other engineers acknowledge that the Northridge earthquake provided an unplanned test of how well steel-frame construction weathers a nearby earthquake. "A significant number of buildings of modern steel construction were subjected to very strong ground motion for the first time," says seismic engineer John Shipp of EQE International Inc. in Irvine. And even though the test was not as tough as it might have been, "they performed poorly."

A nonfatal flaw. The Northridge quake cracked joints in steel-frame buildings, although none collapsed.

None of the buildings identified—more than 100, at distances of up to 25 kilometers from the epicenter—collapsed, but they suffered numerous breaks at connections between the horizontal beams and the vertical columns that form their steel framework. Why these buildings cracked instead of swaying harmlessly isn't clear yet, says Reinhorn, but he and other engineers are considering whether the recent trend toward relying on a few big beams and columns to absorb most of the strain from an earthquake may have been a mistake. The strategy requires unusually large welds, difficult to perform properly under construction-site conditions.

New kinds of steel-frame construction might eliminate such welds, bettering the odds in the next Northridge-sized quake. But that may not be enough, as worse quakes could be in store for the Los Angeles basin. In their paper in this issue, geologist James Dolan of Caltech and his colleagues associated with the Southern California Earthquake Center, headquartered at the University of Southern California, argue that when it comes to major earthquakes, the city has some catching up to do.

By some simple accounting, seismologists have found that the number of earthquakes recorded over the last 200 years seems to fall well short of that expected. The Dolan group studied six major fault systems in the L.A. Basin to determine how much deformation they have undergone over thousands of years as the Los Angeles basin is squeezed by the collision of the Pacific and North American plates. Assuming all the deformation occurred during earthquakes, Dolan and his colleagues conclude the basin must have experienced earthquakes at an average rate much higher than that of the past 200 years. If the quakes were no bigger than Northridge, they must have come every 11 years on average—which would mean, says Dolan, that Los Angeles is long overdue for a spate of Northridges.

The more likely possibility, suggests Dolan, is that most of the slip occurs in a few much larger quakes, with magnitudes of 7.2 to 7.5, that occur every 140 years on average. And in the third paper in this issue, Susan Hough of the USGS in Pasadena lends support to this large-quake alternative. By extrapolating from the frequency of Southern California earthquakes of various sizes, she argues for a mix of moderate and large earthquakes—a half-dozen Northridge-sized ones and one magnitude 7.4 to 7.5 quake every 300 years or so.

The only escape from these grim implications is one explored in a long-awaited report from the Working Group on the Probabilities of Future Large Earthquakes in Southern California, to be released next week. The Working Group, funded primarily by the National Science Foundation and the USGS, considers the possibility that most of the strain on faults beneath the Los Angeles basin is being released quietly, by gradual slip (*Science*, 28 January 1994, p. 460). In that case, there would be no shortfall of earthquakes, and Los Angeles would have nothing worse to fear than it has experienced in recent decades. But now that a second look at Northridge suggests even the status quo is worse than it had seemed, that is likely to be cold comfort to jittery Angelenos.

–Richard A. Kerr

NEUROSCIENCE

A New Face for the Glutamate Receptor

When a baby is born, eager relatives immediately search its face for its father's dimple or its mother's eyes. And in much the same way, biologists examining a newly discovered protein keep a sharp eye out for structural features that may link the protein to its relatives. Such family similarities among proteins are much more than emotionally satisfying: They can be enormously helpful in determining how a protein works. But just as initial appearances among new family members can be deceiving, first impressions of a new protein may turn out to be misleading as well. That is just what happened recently in the case of the proteins that act as receptors for the amino acid glutamate, an important neurotransmitter in the brain.

Five years ago, researchers cloned the first glutamate receptor gene and found that the amino acid sequence of the protein made by the gene resembles those of the receptors for several other neurotransmitters. That led the researchers to predict that the glutamate receptor fits into the cell's outer membrane as those other receptors do, with the protein crossing the membrane four times. The sequence comparison "was all we had to go with at the time," says Stephen Heinemann of the Salk Institute, leader of the team that proposed the original model. But while that was a good working model then, he adds, "I think we were wrong."

Recent work, including findings described in two papers from Heinemann's group in the December issue of *Neuron*, suggests the glutamate receptor has three membrane-spanning segments, not four. If it's correct, this new model will turn the prevailing view of the glutamate receptor on its ear. And many in the field believe it is right. "I think it will be accepted," says Arthur Karlin, who studies receptor structure and function at Columbia University College of Physicians and Surgeons. Evidence against the old model has been accumulating, he says, and most is "consistent with this [new] idea."

In addition to providing a better understanding of the evolution and function of the glutamate receptor, which plays a key role in learning and memory, the new work could have clinical implications. Excess activity of the glutamate receptor contributes to brain damage during stroke and seizure; a better understanding of the receptor could aid in designing drugs to prevent this kind of damage. Beyond that, the about-face has a broader significance: It serves as a warning to protein researchers not to make too much of family resemblances until the baby's parentage has been conclusively established.

Heinemann's group cloned the first gene for a glutamate receptor in 1989 and shortly thereafter came up with their original model of the receptor structure by making use of a "hydropathy plot." This method, a standard for analyzing protein structures, involves searching for fat-loving stretches in a protein's amino acid sequence; such stretches may traverse the cell membrane when the protein assumes its normal configuration within the cell.

When the Salk workers performed a hydropathy plot on the glutamate receptor, they identified four fat-loving segments and therefore proposed that the protein crosses the membrane four times. This arrangement implied that both ends of the protein (the so-called amino- and carboxy-terminals) dangle outside the cell, where they would presumably form the glutamate binding site;

a large loop between transmembrane domains (TMDs) three and four would protrude into the cell.

That structure seemed logical because it had previously been found in several related neurotransmitter receptors, all of which function like the glutamate receptor. Known as "ligand-gated ion channels," these proteins respond to the binding of a neurotransmitter by opening a pore that lets ions flow into the cell. Further support for the idea that glutamate receptors cross the membrane four times came as more glutamate receptor genes were cloned, and all seemed to fit the model. Indeed, many researchers came to accept the model as fact, says neuroscientist Ray Dingledine of the Emory University School of Medicine: "It went unquestioned for years."

Yet some features that were inconsistent with this family resemblance began turning up. By 1993, work from several labs suggested that the carboxy end of the protein was inside rather than outside the cell. That was "the first indication that something was amiss," says Rick Huganir of the Johns Hopkins University School of Medicine, whose lab contributed to that finding.

The next inconsistency arose when the glutamate receptor displayed an unexpected similarity to an entirely different family: a group of bacterial amino acid–binding proteins. In 1990, Richard Axel at the Columbia University College of Physicians and Surgeons and his co-workers found that two small parts of the glutamate receptor resemble parts of a bacterial protein that binds the amino acid glutamine (which is similar to glutamate). That finding drew little attention until 1993, when Patrick O'Hara of ZymoGenetics in Seattle followed up with a more elaborate comparison. The bacterial protein binds glutamine with a clamshell-like structure formed from two separate parts of the protein. O'Hara found broad similarity between the halves of the clamshell and two parts of the glutamate receptor, suggesting that the amino-acid binding sites of the two proteins might be similar.

But there was a problem: In the glutamate receptor, half the clamshell is in the big protein loop. And the old model placed that loop inside the cell, where it could not possibly contact extracellular glutamate. To resolve this paradox, O'Hara proposed, at a meeting in Sicily in the fall of 1993, that the glutamate receptor winds through the membrane an odd number of times, which would put the loop on the cell's exterior. But with the old model so firmly entrenched, this view "was met with skepticism," O'Hara recalls, "and that's putting it nicely."

But more support for this new notion was on its way. Several groups had found that the big loop had sugar-containing glycosyl groups added to some of its amino acids. Because only those parts of membrane proteins destined to be outside of the cell are exposed to the enzymes that add the glycosyl groups, this meant the loop must be outside.

One of the groups that made these findings was that of Robert Oswald at Cornell University in Ithaca, New York. Oswald's team was studying a protein from fish that is related to the glutamate receptor and probably assumes a similar position in the membrane. Spurred by the glycosylation finding,

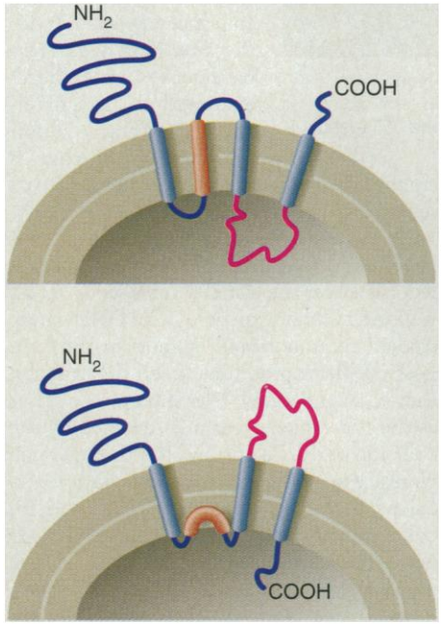

ILLUSTRATION: K. SUTLIFF

About-face. In the new model *(bottom)*, the glutamate receptor crosses the cell membrane three times instead of four, placing the big protein loop outside rather than inside the cell.

Oswald and graduate student Galen Wo examined the hydropathy plots for the proposed transmembrane domains in the fish protein. The second one (TMDII) looked doubtful, says Oswald: "We thought maybe that's not a true membrane-spanning region." So they did an experiment in which they removed that part of the protein. If it were truly a TMD, its loss would reverse the topology of the rest of the protein, placing inside segments outside and vice versa. But deleting the segment had no effect on the topology, suggesting that it does not actually span the membrane. (The results were published last July in *The Proceedings of the National Academy of Sciences*.)

Meanwhile, Michael Hollmann, Cornelia Maron, and Heinemann were working on a systematic test of the glutamate receptor itself to identify parts that are outside the cell. In the work reported in *Neuron*, they introduced synthetic glycosylation sites throughout the protein. They found that all those in the big loop are glycosylated and therefore must be outside the cell. This conclusion was confirmed by a completely different set of experiments by Yael Stern-Bach in Heinemann's lab, in collaboration with O'Hara at ZymoGenetics, which concluded that the large loop is part of the glutamate-binding pocket. "If this is true," says Heinemann, "[the big loop] has to be on the outside of the cell."

The implication of the findings from both Heinemann's and Oswald's groups is that the so-called TMDII does not span the membrane. And now there is direct evidence that that is the case. In a paper coming out in the February issue of *Neuron*, Julie Bennett and Ray Dingledine have shown that both ends of TMDII are rapidly degraded by proteases targeted to the intracellular side of the membrane. That means that while TMDII may sit within the membrane, both its ends emerge from the membrane's intracellular side.

But even though several recent findings support the new model, not all do. For example, Huganir's group and several others have evidence suggesting that the big loop is phosphorylated, and as phosphorylating enzymes act only within the cell, that would mean it must be inside the cell. But Huganir points out that the findings are preliminary, and while they suggest that the phosphorylation sites are within the big loop, that has not been confirmed.

If the model proves correct, says Heinemann, it may upset some major notions about the glutamate receptor. For example, it would mean that the glutamate receptor may not be related to the other ligand-gated ion channels but instead may have evolved from the bacterial amino acid–binding proteins. That would suggest the ligand-gated channels evolved independently at least twice.

There may also be practical consequences from this new model. In previous attempts to understand the function of the glutamate receptor, researchers employed the best understood ligand-gated ion channel—the nicotinic acetylcholine receptor—as a guide. By comparison to that well-known molecule, they guessed which parts of the glutamate receptor bind glutamate, which parts form the ion channel, and which parts are susceptible to chemical alterations that may modify the receptor's behavior. Those key elements form a framework for the design of drugs to curb the receptor's harmful effects in stroke and seizure. Now that framework must be revamped and old assumptions cast aside as new parts of the protein emerge to fill those roles.

But perhaps the true moral of this tale is the broad lesson that a model based on a hydropathy plot is just that: a model that must be verified by experiments. "Don't jump to conclusions," says Dingledine. "There are a lot of assumptions [based on hydropathy plots] that have been built into the textbooks, that have not been properly tested. Here is a very good example where something that was just assumed to be true ... has turned out not to be."

–Marcia Barinaga