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For Immediate Release

**Weill Cornell Scientists Challenge Standard View on Cellular Ion Channel
Functioning**

Computations Point to a More Flexible, Dynamic Mechanism Governing Channel Selectivity

NEW YORK, NY (October 13, 2004) – In any academic arena, it's tough to convincingly challenge a scientific maxim that's so accepted it's been included in textbooks for decades.

But that's what a team of Weill Cornell Medical College biochemists believes they have just done, in a report published in the October 14 issue of *Nature*.

Every living cell contains microscopic ion channels, tiny portals that allow select molecules to pass through the cell's otherwise impermeable, protective outer membrane. Since the 1970s, experts have believed the physical structure of these channels dictates which ions – potassium, sodium, calcium, and others – are admitted, and which are not.

But now, using a computational model, experts led by Weill Cornell's Dr. Benoit Roux say they have proven this long-accepted view wrong.

"We've uncovered unsuspected aspects to this question, and it's possible now to understand ion selectivity from a completely different point of view," said Dr. Roux, professor of physiology & biophysics and professor of biochemistry at Weill Medical College of Cornell University in New York City.

A challenge for researchers investigating the mechanics of ion channels is that their minute size means many facets of their behavior remain inaccessible to direct laboratory investigation.

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However, for decades, biochemists have more or less agreed with the general idea that these channels select specific ions for entry based on their relative diameters. According to this premise, potassium ions – stripped of the usual water molecules that surround them – enter the channel easily, because the cage-like, chemical environment of the channel serves as a replacement for those missing water molecules.

"That's what we might call the 'snug-fit' explanation or view of selectivity," Dr. Roux said.

The view was bolstered in 1998, when X-ray technology allowed the structure of the potassium channel to be determined for the first time at an atomic resolution. That view into the potassium channel revealed dehydrated potassium ions sitting within a narrow tube-like pore, lined by backbone carbonyl oxygen molecules.

"The determination of the X-ray structure is a beautiful advance that had a dramatic impact on our understanding of all ion channels," Dr. Roux said. "However, many people who viewed the channel as a static structure saw that result as a direct confirmation of the 'snug-fit' view of ion selectivity."

But for Dr. Roux, nagging questions remained. He pointed out to colleagues that the difference in size between a potassium and sodium ion was infinitesimally small – less than one-half of an angstrom, a unit used for measurements at the atomic level.

And the potassium channel, like most protein-based structures, didn't turn out to be rigid or static, either. "This tube, that's supposed to be so well-adapted for admitting only the potassium ion, in reality jiggles around enormously," Dr. Roux observed. "In fact, the magnitude of its jiggling around is *larger* than the difference between potassium and sodium."

To the Weill Cornell researcher, this meant that selectivity based solely on the "snug-fit" view wasn't such a good fit, after all.

But what governs selectivity at the microscopic level, then? Science still hasn't come up with technology precise enough to answer this question in the laboratory, so Dr. Roux turned to computer

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simulations instead.

In their computational model, published in *Nature*, Dr. Roux's team proves that selectivity is governed by complex electrostatic relationships between visiting ions and the proteins that make up the ion channel.

"What you discover is that specific chemical groups are surrounding the ion, interacting with it, and that these chemical groups also interact with each other in a way that's dynamic," he explained. "It's a collective relationship that selects out appropriate ions, and guides them through the potassium ion channel."

This new perspective, illuminating one of the most basic of cellular functions, is much more adaptive and dynamic than the long-held "rigid-tube" hypothesis, Dr. Roux said.

"If the previous explanation was right, even the slightest deviation would upset ion trafficking," he said. "Luckily, though, proteins at room temperature act like a jelly; they jiggle around all the time. That's not a flaw, either: It's a blessing, because these proteins are constantly self-correcting as they determine ion selectivity."

In the end, he said, the computation clears up inconsistencies noted in the "snug-fit" explanation.

"We carried out a series of computations that progressively became simpler and simpler, and the final conclusion is very compelling," Dr. Roux said. "This gives us a fresh perspective, allowing us a better understanding of the chemistry of these channels."

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Co-authors include Dr. Sergei Yu Noskov, also of Weill Cornell, and Dr. Simon Berneche, formerly of Weill Cornell and now at the University of Basel, Switzerland.