hosts within a population. Generally, there are two sources of susceptible hosts: births and waning immunity. The latter is a manifestation of either short-lived protection or viruses with different antigenic structure so that hosts who are immune to different viral types can be reinfected. Consequently, viruses that generate long-lasting immunity and cannot generate sufficient diversity within a population are epidemic. For example, measles, mumps, and rubella have very limited antigenic diversity and must wait for births to accumulate before an epidemic can sweep through the susceptible cohort (*2*). But if a virus has sufficient antigenic diversity to enable it to continually reinfect, then why should it be epidemic, and not maintain a constant prevalence all year round?

Pitzer *et al*. address this apparent paradox by showing that births play a role in generating epidemics of rotavirus, and use this result to predict the impact of vaccination. A corollary of their findings is that first infections (not reinfections) are intrinsically important to viral persistence in a population, so that reducing these to negligible levels through mass childhood vaccination will eliminate an endemic virus.

However, one cannot firmly conclude that infection of susceptible hosts (newborns) is chiefly responsible for driving the intrinsic epidemic cycle of rotavirus or respiratory syncytial virus. There is a dynamic interaction between host demography and viral diversity that determines epidemiology (*3*), so that epidemics may be created, or at least influenced, by strain variation (*4*). In developing countries, rotavirus is less seasonal than in the United States and Europe, perhaps influenced by higher birth rates. But the very high diversity of co-circulating rotavirus variants in Africa and other developing countries (*5*) could indicate that reduced seasonality results from more continuous reinfections by antigenically different variants. Furthermore, contact patterns (that determine which viruses are circulating in a particular subgroup) vary (*6*), and are likely to be different in developing countries (although specific data are currently lacking) and to vary with social circumstances and situation, including birth rate and contact between children and adults. This is a complex situation about which we understand little, although the impact of vaccination will be revealing.

There are two possible, general outcomes to vaccination (*7*). One is that a vaccine will effectively reduce viral prevalence, disease, and diversity. If first infections are critical for rotavirus persistence, then reinfections and viral diversity are essentially bystanders. The other outcome is that the vaccine will reduce disease, but viral prevalence will remain unchanged. If rotavirus can survive in a population of already infected hosts, then, although diversity might be altered, it will remain high, and prevalence unaltered.

Current approaches to vaccines, particularly live-attenuated vaccines, may be less effective in malnourished populations with high rates of infection (and superinfection) and may also be compromised by the presence of maternal antibodies or immunological immaturity, so that very young children are less easy to protect. If there are substantial vaccine failures or the proportion of the population that is vaccinated is low, or if there is a need to vaccinate older age groups, then continued circulation of virus is unwelcome. So if the last situation pertains, then there is a rationale for developing sterilizing vaccines that prevent reinfections.

Endemic infections generally are well adapted to their environments, which extend from the biologic into the economic, social, and political spheres. Because RNA viruses such as rotavirus and respiratory syncytial virus are highly adaptive, changes (such as birth rates) and interventions (such as vaccination) will have long-term consequences that are difficult to predict and might be serious.

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PHYSICS

Is Quantum Theory Exact?

Future experiments may tell us if quantum mechanics is an approximation to a deeper-level theory.

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Quantum mechanics has enjoyed many successes since its formulation in the early 20th century. It has explained the structure and interactions of atoms, nuclei, and subnuclear particles, and has given rise to revolutionary technologies, such as integrated circuit chips and magnetic resonance imaging. At the same time, it has generated puzzles that persist to this day.

These puzzles are largely connected with the role of measurements in quantum mechanics (*1*). According to the standard quantum postulates, given the total energy (the Hamiltonian) of a quantum system, the state of the system (the wave function) evolves with time in a predictable, deterministic way as described by Schrödinger's equation. However, when a physical quantity—the quantum mechanical spin, for example—is "measured," the outcome is not predictable. If the wave function contains a superposition of components, such as spin-up and spin-down (each with a definite spin value, weighted by coefficients c_{up} and c_{down}), then each run gives a definite outcome, either spin-up or spin-down. But repeated experimental runs yield a probabilistic distribution of outcomes. The outcome probabilities are given by the absolute value squared of the corresponding coefficient in the initial wave function. This recipe is the Born rule.

How can we reconcile this probabilistic distribution of outcomes with the deterministic form of Schrödinger's equation? What precisely constitutes a "measurement?" At what point do superpositions break down, and definite outcomes appear? Is there a quantitative criterion, such as size of the measuring apparatus, governing the transition from coherent superpositions to definite outcomes? These puzzles have inspired a large literature in physics and philosophy.

There are two distinct approaches. One is to assume that quantum theory is exact, but that the interpretive postulates must be modified to eliminate apparent contradictions. The second approach is to assume that quantum mechanics is not exact, but instead is a very accurate approximation to a deeper-level theory that reconciles the deterministic and probabilistic aspects. This may seem radical, even heretical, but looking back in the history

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of physics, there are precedents. Newtonian mechanics was considered to be exact for several centuries, before it was supplanted by relativity and quantum theory. But apart from this history, there is another important motivation for considering modifications of quantum theory. Having an alternative theory, to which current and proposed experiments can be compared, allows a quantitative measure of the accuracy to which quantum theory can be tested.

We focus here on phenomenological approaches that modify the Schrödinger equation. A successful phenomenology must accomplish many things: It must explain why repetitions of the same measurement lead to definite, but differing, outcomes, and why the probability distribution of outcomes is given by the Born rule; it must permit quantum coherence to be maintained for atomic and mesoscopic systems, while predicting definite outcomes for measurements with realistic apparatus sizes in realistic measurement times; it should conserve overall probability, so that particles do not spontaneously disappear; and it should not allow superluminal transmission of signals.

Over the past two decades, a phenomenology has emerged that satisfies these requirements. One ingredient is the observation that rare modifications, or "hits," acting on a system by localizing its wave function, do not alter coherent superpositions for microscopic systems, but when accumulated over a macroscopic apparatus can lead to definite outcomes that differ from run to run (*2*). A second ingredient is the observation that the classic "gambler's ruin" problem in probability theory gives a mechanism that can explain the Born rule governing outcome probabilities (*3*). Suppose that Alice and Bob each have a stack of pennies, and flip a fair coin. If the coin shows heads, Alice gives Bob a penny, while if the coin shows tails, Bob gives Alice a penny. The game ends when one player has all the pennies and the other has none. Mathematical analysis shows that the probability of each player winning is proportional to the size of their initial stack of pennies. By mapping the initial stack sizes into the modulus squared of the initial spin component coefficients (c_{up} and c_{down}), and the random flips of the fair coin into the random "hits" acting on the wave function, one then has a mechanism for obtaining the Born rule.

The combination of these two ideas leads to a definite model, called the continuous spontaneous localization (CSL) model (*4*), in which a Brownian motion noise term coupled nonlinearly to the local mass density is added to the Schrödinger equation. This noise is responsible for the spontaneous collapse of the wave function. At the same time, the standard form of this model has a linear evolution equation for the noise-averaged density matrix, forbidding superluminal communication. Other versions of the model exist (*5*, *6*), and an underlying dynamics has been proposed for which this model would be a natural phenomenology (*7*).

The CSL model has two intrinsic parameters. One is a rate parameter, λ, with dimensions of inverse time, governing the noise strength. The other is a length, r_C, which can be interpreted as the spatial correlation length of the noise-field. Conventionally, r_C is taken as 10^{-5} cm, but any length a few orders of magnitude larger than atomic dimensions ensures that the "hits" do not disrupt the internal structure of matter. The reduction rate in the CSL model is the product of the rate parameter, times the square of the number of nucleons (protons and neutrons) within a correlation length that are displaced by more than this length, times the number of such displaced groups. Applying this formula, and demanding that a minimal apparatus composed of $\sim 10^{15}$ nucleons should settle to a definite outcome in $\sim 10^{-7}$ s or less, with the conventional r_C, requires that λ should be greater than $\sim 10^{-17}$ s^{-1} (*4*, *5*). If one requires that latent image formation in photography, rather than subsequent development, constitutes a measurement, the fact that only 5000 or so nucleons move appreciable distances in a few hundredths of a second in latent image formation requires an enhanced lower bound for λ a factor of $\sim 10^8$ larger (*8*).

Upper bounds on λ

Laboratory experiments	Decades above the conventional value
Fullerene diffraction experiments	13
Decay of supercurrents	14
Spontaneous x-ray emission from Ge	6
Proton decay	18
Mirror cantilever interferometric experiment	9
Cosmological data	**Decades above the conventional value**
Dissociation of cosmic hydrogen	17
Heating of intergalactic medium (IGM)	8
Heating of interstellar dust grains	15

Quantum boundaries. Upper bounds on λ obtained from laboratory experiments and cosmological data, compared with the conventional CSL model value $\lambda \sim 10^{-17}$s^{-1} (with noise correlation length, $r_C = 10^{-5}$ cm). Reducing the numbers by 8 gives the distance of each bound from the enhanced value $\lambda \sim 10^{-9}$ s^{-1} obtained if one assumes that latent image formation constitutes measurement.

An upper bound on λ is placed by the requirement that apparent violations of energy conservation, taking the form of spontaneous heating produced by the noise, should not exceed empirical bounds, the strongest of which comes from heating of the intergalactic medium (*8*). Spontaneous radiation from atoms places another stringent bound (*9*), which can, however, be evaded if the noise is nonwhite, with a frequency cutoff (*10–12*). Laboratory and cosmological bounds on λ (for $r_C = 10^{-5}$ cm) are summarized in the figure, which gives for each bound the order of magnitude improvement needed to confront the conventional CSL model value of λ.

Accurate tests of quantum mechanics that have been performed or proposed include diffraction of large molecules in fine mesh gratings (*13*) and a cantilever mirror incorporated into an interferometer (*14*). The figure shows the current limit on λ that has been obtained to date in fullerene diffraction and the limit that would be obtained if the proposed cantilever experiment attains full sensitivity (*15*). To confront the conventional (enhanced) value of λ, one would have to diffract molecules a factor of 10^6 (10^2) larger than fullerenes.

Experiments do not yet tell us whether quantum theory is exact or approximate. Future lines of research include refining the sensitivity of current experiments to reach the capability of making this decision and achieving a deeper understanding of the origin of the CSL noise field.

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