protein found in inhibitory synapses (*2*). Unlike the direct binding between neuroligin and PSD-95, there is no known interaction between neuroligins and gephyrin, so additional undiscovered factors need to be invoked for the specification of inhibitory synapses.

Why should NL-2 behave differently from NL-1 and NL-3? An intriguing clue is that the level of PSD-95 (which binds to all three neuroligin isoforms) seems to determine whether inhibitory or excitatory synapses are made (*3*). Overexpression of PSD-95 recruited more neuroligin to glutamate synapses and reduced the relative number of GABA synapses. Conversely, suppression of PSD-95 increased inhibitory synapses at the expense of excitatory synapses (*3*). If NL-2 binds less well or is less accessible to PSD-95, then this could explain its propensity for inducing inhibitory synapses.

Whatever the precise mechanism, their double duty as inducers of either excitatory or inhibitory synapses places β-neurexins and neuroligins center stage in the control of excitation/inhibition (E/I) balance, which is critical for neuronal function (*7*). Indeed, neurons deficient in neuroligins displayed an abnormal E/I balance, with greater loss of inhibition than of excitation (*1*). Genetic mutations in NL-3 and -4 have been implicated in human mental retardation and autism (*8–10*). Could these illnesses be due to an E/I imbalance resulting from aberrant formation of excitatory versus inhibitory synapses? Genetic experiments in which individual β-neurexin and neuroligin isoforms are disrupted in animal models are essential to explore this idea and to confirm the conclusions reached by the intriguing in vitro studies discussed here.

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HISTORY OF SCIENCE

"How Science Survived"—Medieval Manuscripts as Fossils

Sharon Larimer Gilman and Florence Eliza Glaze

Ancient texts survived from Antiquity through the Middle Ages as manuscript copies produced by monks and professional scribes until the invention of the printing press in the 15th century A.D. Many of these texts are still in existence today, having battled an astonishing array of hazards including fire, war, theft, and neglect. But how can we calculate the percentages of texts that have survived or gone extinct and consequently the amount of knowledge that we have inherited from Antiquity and the Middle Ages? On page 1305 of this issue, Cisne (*1*) takes a unique and stimulating approach to solving this dilemma by linking the paleodemography of such texts to population dynamics. Cisne took a small number of extant medieval scientific manuscripts, such as Bede's *De Temporum Ratione* from 725 A.D., and examined them as "fossils" of early textual "populations." Applying models used by population biologists, Cisne calculated the size and age-distributions of these scientific texts. His work provides a wonderful example of the potential value of collaboration between the arts and sciences.

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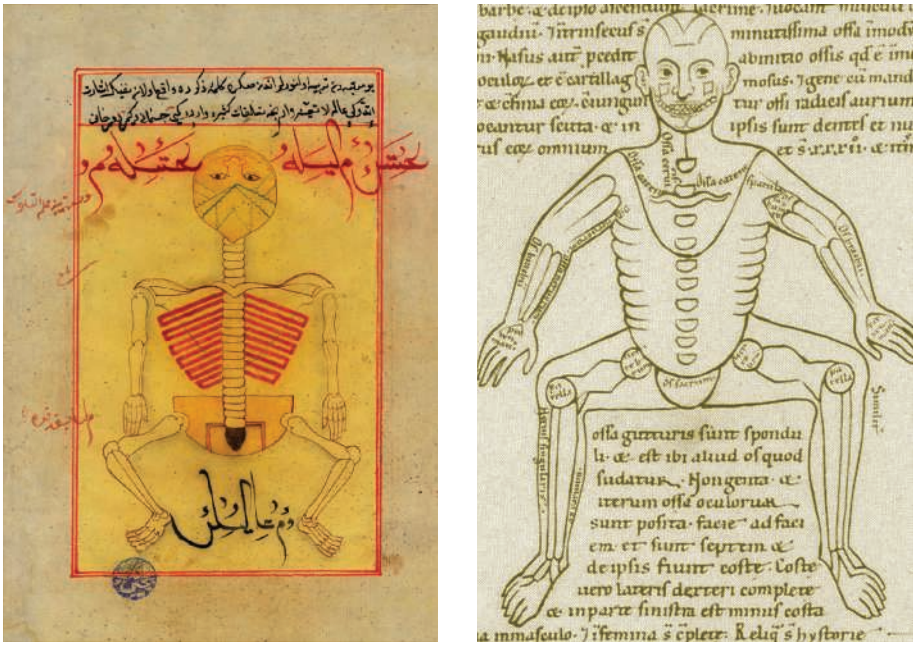
Cisne applied two models from population biology to assess the survival and rate of expansion of textual populations of medieval manuscripts. These models are the Verhulst-Pearl logistic model of population growth, and the Markov birth-and-death process (where birth equals the production of new copies of texts, and death means the destruction of such texts). According to these models, the population of manuscripts increases logistically based on the standing population at any one time, taking into account birth and death rates. This works for medieval manuscripts because they are individually copied; the more there are, the faster they can reproduce, just as with a living (or a once-living) population. The rate of population growth slows as the population reaches its carrying capacity. For living organisms, this would be largely the result of increased competition for resources. For the manuscripts, it is a combination of the decline in demand for and the rate of destruction of the manuscript. The population biology models used by Cisne tend to apply best to populations of organisms with the simplest of life-histories, but the author makes a compelling case that at least some medieval manuscripts appear to have similarly simple "life-histories." The Cisne study offers a potentially useful tool to examine those histories, provided that certain modifications are applied—for the history of manuscripts isn't quite as simple as the model assumes.

To begin with, certain statements and the assumptions they betray in the Cisne report require explicit correction. It is scarcely true that, in Cisne's words, "the germ of…science barely made it through the Middle Ages." On the contrary, from the 12th through 15th centuries, science and scientific medicine constituted two of the most vigorous disciplines pursued in universities across Europe (*2*). Most Greek scientific and medical literature surviving today from the ancient world was recovered during this period, the texts of Aristotle and Galen being the best examples. In addition, new manuscripts were avidly sought and translated—both from Greek and Arabic—and these texts were commented upon in the university system that was itself a forum for discourse and disputation invented by medieval scholars (*3*). The sorry state of scientific studies at the close of the Roman Empire in the fifth century reflected Roman, not medieval, failures and shortcomings (*4*). Although the Latin language was capable of communicating scientific ideas, most Romans showed little interest in wholesale scholarly translations from Greek (*5*). The precipitous decline in Greek literacy among the Latinate population in the Western Empire by the 3rd century created a crisis in the transmission of scientific literature that was only corrected in the 12th century, after the many disruptions of the early Middle Ages had subsided and the secular school had been reborn (*6*). Cisne correctly guesses that the leap from papyrus to parchment in late Antiquity was one crucial element in the survival of texts, but there were many others (*7*). Finally, high-to-late medieval enthusiasm for science suffered at the close of the Middle Ages, when humanists of the Renaissance turned away from scientific studies (*3*, *8*). Many humanists impugned the scientific tradition derived from Islam, and only came to embrace science in the 16th century after leading theorist-practitioners had adopted the humanists' own classicizing methods.

Having dispelled somewhat the widely held myth that the Middle Ages were a "dark age" for science, we can explore the possibilities as well as potential shortcomings of Cisne's methods. Two of the model's assumptions hold up well to scrutiny. The first is that the "population" responds immediately to changing conditions (that is, there is no time-lag to the response as might be the case with a population of living organisms); the second is that all individuals are equivalent from a quantitative perspective. Qualitatively, however, we must remember that a textual fragment can never reproduce a full, integral copy. Moreover, neither a constant environment, a closed population, nor a constant rate of text destruction (death rate) seem valid assumptions to us. Regarding the constant environment and probable half-life, there were more violations than could easily be enumerated. Many texts enjoyed a very limited circulation, owing in part to their complex theoretical language and verbosity. Others were written in regional, highly calligraphic scripts, with peculiar abbreviations and letter-forms, and therefore remained isolated or indecipherable when transported elsewhere. Death rate was inconstant, and due to many factors: intentional destruction, theft, neglect, erasure, mishandling by Renaissance printers, and modern disasters intended and accidental. Some population sites, such as monasteries, were safer than others; there are no survivors of privately owned scientific manuscripts before the 12th century. Centuries of military action in regions like the Rhineland extinguished entire collections.

Neither, as Cisne's model assumes, was the population of medieval scientific manuscripts an entity closed to immigration and emigration. Quite the opposite, in fact. From the 11th century onward, new translations made by North African and European scholars from outside populations in the Byzantine and Islamic realms were transmitted across Europe, replacing in popularity and sophistication the earlier texts from Carolingian times (late 8th to early 10th century A.D.). The earlier population of texts survived mainly in private or monastic collections, and was not considered suitable for scholastic studies. Even scientific illustrations were transmitted, sometimes "translated," as they entered the Latin West from the eastern Mediterranean. An example of this process can be seen in the anatomical text known as "the 5-Figure Series," which entered Europe in the 12th century (*9*) (see the figure).



The art of translation. Populations of medieval scientific manuscripts were open to immigration and emigration. Scientific illustrations often were transmitted, or sometimes even "translated," as they entered the Latin West from the eastern Mediterranean. An example of this process can be seen in the anatomical text known as the "5-Figure Series," which entered Europe in the 12th century (*9*). (**Left**) A modern Turkish copy of a medieval Arabic anatomy figure from the 5-Figure Series, in traditional "dissection" pose. (**Right**) A 12th-century Latin Romanesque "translation" of the same figure.

It might behoove Cisne to refine his study by limiting and defining the focal population more carefully. Much of his evidence examines the texts that were current in the Carolingian period, which were produced before the influx of new translations after 1050 A.D. If Cisne explicitly confined his study to this population, tracing its survival in later medieval manuscripts, his assumptions would suffer fewer violations. He might also consider enumerating a broader series of texts and their representative witnesses as his sampling. Both his figures and tables on Bede's texts show remarkable promise for understanding the population's dynamic changes over time. To these, Cisne might add Pliny in his various manifestations, including the many witnesses of the *Medicina Plinii*, and the late ancient medical encyclopedists Oribasius and Alexander of Tralles. Even the early Latin translations of the Hippocratic *Aphorisms* have now been enumerated sufficiently that the population of these texts might well demonstrate the further conclusiveness of Cisne's demographic calculations and projections (*10*).

Ultimately, Cisne's ambitious efforts to analyze surviving medieval scientific manuscripts as "fossils" offers the field of manuscript scholars the opportunity to estimate and envision within a reasonable margin of error the rate of expansion of textual populations. Cisne's approach inspires us, moreover, to consider issues that might not ordinarily present themselves, including sociocultural factors like "carrying capacity" and "predation." For his efforts, and these provocative insights, manuscript scholars owe Cisne a very real debt of gratitude.

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