replaced at another time by interaction to a different partner. In contrast, interactions to multi-interface hubs may be persistent, and might therefore reflect necessity.

The idea that multi-interface hubs are more highly integrated into cellular networks may also affect the issue of horizontal gene transfer as an evolutionary mechanism. It has been argued that the more integrated a protein is into cellular organization, the less likely it is that a horizontally transferred gene will displace it (14). It will be interesting to see if there is a notable difference in horizontal gene transfer tendencies between single-interface and multi-interface hubs.

After years of fruitful work in systems biology, network analysis, bioinformatics, and structural genomics, cross-fertilization of these inherently related perspectives is beginning to take place (15). The work of Kim et al. shows the shift toward increased integration of multiple perspectives. Future progress in understanding cellular networks will require more complete data sets describing the underlying interactions. A knowledge of which proteins are interacting in the yeast cell is approaching some degree of completion, but only a fraction of those interactions can presently be mapped onto protein surfaces in three dimensions, which is required for the analysis developed by Kim et al. The insights drawn by their methods of analysis will be further strengthened as more structural data become available.

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Recent molecular evidence suggests that

crustaceans may have successfully invaded

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EVOLUTION The Origin of Insects

Henrik Glenner, Philip Francis Thomsen, Martin Bay Hebsgaard, Martin Vinther Sørensen, **Eske Willerslev**

lthough hexapods-those arthropods having six legs, including insectsare the most diverse group of contemporary animals in terms of biological niches and number of species, their origin is highly debated. A key problem is the almost complete absence of fossils that connect hexapods to the other major arthropod subphyla, namely Crustacea, Myriapoda (such as centipedes and millipedes), and Chelicerata (such as scorpions and spiders). Over the years, hexapods (insects, springtails, proturnas, and diplurans) have been phylogenetically linked to all of these major arthropod taxa (1).

Traditionally, hexapods and the multilegged myriapods have been united in a group named Atelocerata on the basis of morphological similarities between their tracheal respiration systems and head appendages. However, recent evidence from phylogenetic analyses of molecular sequence data from a variety of genes, as well as from newer morphological studies, points to a relationship between hexapods and crustaceans (2-9), a grouping commonly referred to as Pancrustacea. Furthermore, studies on neurological development in the major arthropod groups have pointed out similarities between the myriapods and cheHexapod

land as insects.



Hexapod evolution. The last common ancestor of hexapods and crustaceans (branchiopods, specifically) may have originated in freshwater during the Late Silurian, giving rise to extant freshwater dwelling branchiopods (fairy shrimps, water fleas, and tadpole shrimps) and insects. This hypothesis accounts for the missing fossil record of branchiopods and hexapods before the Devonian.

licerates (10). Hence, pancrustacean monophyly seems to be gaining more support. So, what does this view tell us about the possible origin of hexapods?

The crustaceans are recorded at least as far back as the Upper Cambrian, about 511 million years ago (11), where they are found in marine sediments (see the figure). However, except for the debated Devonohexapodus bocksbergensis specimen (12, 13), all hexapod remains are found only in freshwater or terrestrial strata no earlier than the Devonian. around 410 million years ago (14). This leaves a gap of 100 million years to the earliest crustaceans. The common explanation has been that earlier traces of hexapods have been erased from the fossil record and that hexapods, like other major groups of terrestrial animals, have closely related ancestors to be found in the marine environment.

The recent morphological and molecularbased studies suggest an alternative interpretation-that hexapods originated within the crustaceans rather than as a sister group (15-20). Although the morphological studies mainly favor a close phylogenetic connection between Downloaded from www.sciencemag.org on March 6, 2007

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PERSPECTIVES

hexapods and malacostracan crustaceans (crabs and crayfish) (15, 16), recent molecular sequence data suggest that hexapods are closely related to branchiopods (17, 19, 20), a freshwater dwelling group of crustaceans that includes water fleas and fairy shrimp. This hypothesis is supported by analysis of Hox genes that demonstrates homology between development of the pregenital trunk region in insects and the thorax in branchiopods (21). The new molecular results correspond well with the fossil record and suggest an evolutionary origin of the hexapods in freshwater around 410 million years ago rather than in the marine Cambrian environment (17).

The vast majority of extant branchiopods are freshwater animals, and the few that are found in saltwater are believed to have invaded the sea secondarily. From the fossil record, it is known that modern branchiopods date back to the Early Devonian, by which time they were fully adapted to freshwater habitats (22). This late appearance of the freshwater branchiopods corresponds exactly with the emergence of hexapods and suggests that their last common ancestor swam around in a freshwater pond sometime in the Late Silurian (423 to 416 million years ago) or Early Devonian. This corresponds well with the time split between the crustacean and hexapod lineages estimated from molecular clock analyses (23). If correct, the early marine ancestor of the hexapods might have appeared more similar to Rehbachiella kinnekullensis, a close marine relative to branchiopods from Upper Cambrian (24), than to D. bocksbergensis or other hexapods.

The successful colonization of the terrestrial environment by hexapods seems to coincide with other major groups of land pioneering animals such as the chelicerates and the myriapods in the Late Silurian and the tetrapods (amphibians, reptiles, birds, and mammals) in the Late Devonian. All these events appear to have occurred through a freshwater dwelling phase in their evolutionary transition from marine to true terrestrial animals. The Devonian is believed to have been a time of severe drought, which might have forced these animals (at least hexapods and tetrapods) onto land as their freshwater habitats vanished.

It has been a puzzle as to why hexapods in particular insects, which possess a morphology that apparently enables them to adapt to virtually all types of terrestrial environments—have not been able to diversify successfully in the marine environment. It is likewise remarkable that the crustaceans fulfilling a biological role in the sea comparable to the insects on land—have not been able to invade land to a greater extent despite their considerable age. The recent phylogenetic analyses of molecular sequence data suggest a paradigm shift concerning the phylogenetic position of hexapods-that crustaceans successfully invaded land as insects. It is possible that when insects entered terrestrial habitats, their crustacean ancestors had already diversified in marine environments and occupied all potential niches, which could explain why insects were prevented from colonizing the sea subsequently. Most important, however, the new molecular results offer a solution to the enigma concerning the absence of marine hexapod remains in the fossil records prior to the Devonian.

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EPIDEMIOLOGY

Influenza Escapes Immunity Along Neutral Networks

Erik van Nimwegen

Given that influenza virus continues to escape immunity, why is it that only one strain dominates each year? The answer may lie in neutral networks and mapping viral genotypes to antigenic phenotypes.

n the late 1960s, Kimura (1) made the then-revolutionary proposal that many L amino acid substitutions are neutral in terms of evolutionary selection. There is now little doubt that essentially any genotype can undergo a substantial number of amino acid substitutions without substantially changing its fitness. This implies that there are large collections of selectively neutral genotypes that are connected through point mutations. Indeed, such "neutral networks" are observed in genotype-to-phenotype mappings of biomolecules (2, 3). On page 1898 of this issue, Koelle et al. (4) provide compelling evidence that neutral networks play a key role in the evolution of human influenza A (H3N2).

Computer simulations and analytical studies (5-7) have shown that intertwined neutral networks have profound conse-

quences for evolutionary adaptation. Evolving populations typically exhibit "epochs" of phenotypic stasis, punctuated by sudden changes in phenotype. However, phenotypic stasis is not accompanied by genotypic stasis. During each phenotypic epoch, the population is dominated by genotypes belonging to one neutral network, and neutral mutations cause the population to drift continuously through this neutral network (see the figure). Mutations to neighboring neutral networks (those networks that can be reached by a point mutation from one of the genotypes in the current neutral network) occur as well and enable the population to explore other phenotypes until, eventually, a mutant on a neutral network with higher fitness is generated. The offspring of this beneficial mutant will then spread through the population, causing a sudden shift in phenotype. Until the study by Koelle et al., this "epochal evolution" scenario (see the figure) had been observed mostly in silico and from in vitro evolution experiments (5-8).

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