shaping the composition of both the Earth's surface and its interior. Water released by dehydration could carry away much of the soluble-element content of subducting crust and sediment. Any prediction of the composition of deeply recycled crustal material must take account of these losses. ■

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Virus evolution

The importance of being erroneous

Sebastian Bonhoeffer and Paul Sniegowski

Viruses must mutate to survive in the face of attack by their host's immune system. A new model suggests that the viral mutation rate is optimized in an evolutionary trade-off between adaptability and genomic integrity.

Evolution by natural selection requires genetic variation, and the ultimate source of this variation is mutation — random errors in genomic replication. In fact, because the fidelity of genomic replication is influenced by genetic variation, the mutation rate is itself subject to natural selection. Broad taxonomic data are consistent with this idea. Although mutation rates per nucleotide vary by factors of up to a million among living things, the variation in genomic mutation rates is less than a factor of a thousand. In RNA viruses, roughly one nucleotide per genome is incorrectly reproduced in each replication; for retroviruses this genomic mutation rate is one per ten replications; and it is one per 300 replications in DNA-based microbes, including DNA viruses and microorganisms[1]. Indeed, the remarkable similarity of genomic mutation rates within each of these groups may reflect deep underlying selective constraints, but its explanation remains a challenge to evolutionary biologists.

Writing in the journal *Complexity*, Christel Kamp and colleagues[2] have now tackled the evolution of genomic mutation rates from a fresh angle. By incorporating the immune response as an explicit selective force in standard 'quasispecies' models, they calculate a viral genomic mutation rate that optimally balances the costs of too much and too little genetic variation.

Quasispecies theory[3] was developed over 30 years ago as a means of describing evolution in populations of self-replicating RNA molecules with high mutation rates (quasispecies is the term applied to closely related genetic sequences that are affected as a group by natural selection). But it was soon recognized that quasispecies theory made a useful tool for the study of viral evolution. Its most fundamental prediction is the existence of an error threshold. If the mutation rate exceeds this threshold, then all genomic information is irretrievably lost and the population becomes extinct in a kind of mutational meltdown. In standard quasispecies theory, the simplifying assumption is made that evolutionary fitness is entirely genetically determined and thus constant irrespective of the environment. Under this assumption, a zero mutation rate is optimal and selection should always favour greater fidelity of replication.

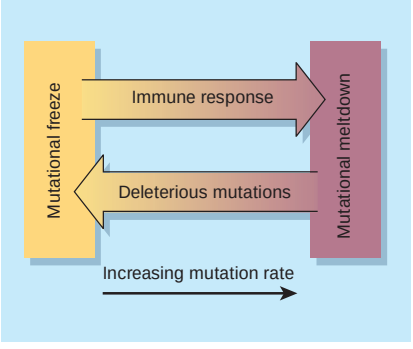

Figure 1 **The evolution of viral genomic mutation rates. High mutation rates may enable viruses to escape the host's immune responses, but low mutation rates reduce the probability of destroying essential viral genes. If the mutation rate is too high or too low, the viral population becomes extinct either because the genetic information is irretrievably lost or because the population cannot keep pace with the immune response. Kamp *et al.*[2] have calculated a genomic mutation rate that optimally balances these constraints.**

But viruses in their natural environments typically face rapidly changing selection pressures as, for example, exerted by the immune response of the body under viral attack. So Kamp *et al.*[2] have extended quasispecies theory to incorporate an adaptive immune response. In such an environment, a quasispecies becomes subject to a second mutational threshold, this time a kind of mutational 'freeze': if the mutation rate is too low, then the quasispecies does not keep pace with environmental change and becomes extinct. An optimal genomic mutation rate must therefore lie somewhere between mutational freeze and mutational meltdown (Fig. 1).

Kamp *et al.* have calculated this optimal genomic mutation rate by finding the mutation rate that maximizes viral growth rate in the presence of an immune response. They find that the optimal mutation rate is given by the ratio of the timespan required for the virus to go through an entire replication cycle to the timespan for the immune system to mount a response to a new viral mutant. This result is reminiscent of population-genetic theories that have concluded that a rate of mutation that mirrors the rate of change of the selecting environment is optimal for adaptive evolution[4–6].

But Kamp *et al.* go one better than these earlier models in that they incorporate the immune response as an explicit selective force. Comparing their quantitative predictions with data for viral genomic mutation rates, they suggest that many viruses, including HIV, replicate at the optimal genomic mutation rate. Interestingly, their result offers an explanation for the intriguing constancy of genomic mutation rates within viral classes, because the variation in the duration of viral life cycles and the time to mount an immune response is probably considerably smaller than the variation in the rates of mutation per nucleotide.

The idea that viral mutation rates are optimal for escaping host immune responses is appealing[7], but some questions remain. First, as previously mentioned, genomic mutation rates in RNA viruses are ten times higher than in retroviruses and 300 times higher than in DNA viruses. This doesn't fit the hypothesis of Kamp *et al.*, because there is no clear evidence for systematic differences in the duration of viral life cycles or the dynamics of the immune responses to these classes of virus. Second, escape from the immune system is not a universal feature of viruses: many viruses may survive by transmission to new hosts before the immune response takes effect.

In addition, the model of Kamp *et al.* forgoes some of the realism of population-genetic models for the evolution of mutation rates (reviewed in ref. 8). Such models explicitly consider the fate of genes that modify replication and repair — changes in the frequency of these modifier genes, due to the rise or fall of linked beneficial or deleterious mutations, affect the evolution of the

mutation rate. This indirect selective force is considerably weakened by genetic recombination, a process that breaks apart linked genes — and a factor not included by Kamp *et al.* in their model. But recombination is substantial in many viruses, and its effect should probably be considered explicitly in modelling the evolution of viral mutation rates.

Despite these shortcomings, the paper of Kamp *et al.*[2] is clearly an important conceptual development in the study of mutation-rate evolution in viruses. Moreover, developing a fuller understanding of the evolutionary causes and consequences of viral mutation rates is worthwhile from both basic and applied perspectives. Drugs that increase genomic mutation rates can kill off viral populations by causing them to exceed their error threshold[9,10]. A quantitative theory that can predict how close to the error threshold a given viral population is — without the need to estimate its mutation rate directly — might have real therapeutic value. ■

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Plant biology

Fixation with regulation

J. Allan Downie and Martin Parniske

A gene has been isolated that controls the number of symbiotic nitrogen-fixing nodules in legumes. Its similarity to a well-characterized regulatory gene in *Arabidopsis* provides clues about its action.

Leguminous plants produce root nodules, within which symbiotic bacteria capture atmospheric N_2 and convert it into nitrogen that can be used by the plant. But this process is energetically expensive and so legumes strictly control the numbers of nodules they form. Papers by Krusell *et al.*[1] and Nishimura *et al.*[2] (pages 422 and 426 of this issue), and by Searle *et al.*[3] in *Science*, describe the characterization of a regulatory gene that normally limits nodule numbers, and that when mutated increases nodulation. Control of nodule development is of interest in its own right, but this work may also have agricultural applications.

Soybean and pea mutants with enhanced nodulation have been known for about 20 years[4], but their complex genomes have hampered attempts to clone the genes responsible. Similar mutants[5,6] were recently identified in *Lotus japonicus*, a legume with a relatively small genome. These mutants have hypernodulation and aberrant roots, hence their designation as *har* mutants. The numbers of both nodules and lateral roots are increased in these *L. japonicus* and soybean mutants, indicating that normal legumes possess a common regulatory mechanism that limits the numbers of root and nodule growing points, or meristems.

Grafting experiments showed that *HAR1* control of nodule and lateral-root number in *L. japonicus* depends on the shoots rather than the roots (Fig. 1, overleaf), a characteristic that had been previously observed with soybean hypernodulation mutants[4]. So plants with *har1*-mutant shoots grafted onto wild-type roots had increased root nodulation. In contrast, the reciprocal grafted plants (mutant roots with wild-type shoots) had normal roots and nodules. After positioning *HAR1* on a physical map of the *L. japonicus* genome, two groups[1,2] cloned the gene. They went on to identify mutations in the equivalent genes in pea[1] and soybean[2] hypernodulation plants, which showed a similar shoot control of nodulation[3]. Independently, following about 15 years of work[3], the equivalent gene controlling nodulation in soybean was isolated and was called *NARK* (nodule autoregulation receptor kinase). It is clear that *HAR1* and *NARK* are the same genes from different species.

HAR1 and *NARK* encode a type of receptor protein that is abundant in plants[7] and has three components: an extracellular domain of leucine-rich repeats, a membrane-spanning domain, and an intracellular protein kinase domain (Fig. 2). This structure is compatible with the receptor's function being perception of a ligand outside the cell, followed by internal signal transduction through protein phosphorylation by the kinase domain. Mutant genes sequenced from the three species had

100 YEARS AGO

We have received from Mssrs. J. W. Gray and Son a pamphlet on scientific protection against lightning, written by Mr. A. Hands. The writer gives a careful explanation of the principles which must be observed in erecting lightning conductors; as the pamphlet is written in non-technical language, it is to be hoped it may be the means of disseminating information amongst the public, since there are few subjects on which more ignorance and superstition exist. The importance of careful protection may be gathered from the fact that Mr. Hands estimates the damage caused annually by lightning in this country alone at from 50,000*l.* to 100,000*l.*

ALSO

The Liverpool correspondent of the *Central News* states that the Nobel prize of 3,000*l.* for researches in connection with malaria will be a personal one to Major Ross, principal of the Liverpool School of Tropical Medicine. According to the Stockholm correspondent of the *Daily Chronicle*, the prize for medicine will be awarded to Prof. Finsen, the Danish discoverer of the treatment by red light for lupus, and the prize for physics to Prof. S. A. Arrhenius.
From *Nature* 27 November 1902.

50 YEARS AGO

On November 4 at 16h. 58m. 20s. G.M.T., an earthquake occurred with epicentre… near the east coast of Kamchatka. It was recorded strongly at seismological observatories throughout the world and had a magnitude of $8^1/_2$ on the Gutenberg–Richter logarithmic scale… Faulting probably took place in the sea bed near the epicentre since a great tsunami or seismic sea wave resulted, and spread throughout the Pacific Ocean. It arrived at the coast of northern Japan about 20h. G.M.T. on November 4. The Hawaiian warning system was used and the coastlines of several islands, including the Oahu coast, were evacuated in anticipation of the wave. When the wave arrived at Hawaii itself, it is reported to have been several feet high… Waves from one to three feet high arrived at the Whangarei beaches in the north of New Zealand about 7 p.m. local time on November 5. When these waves arrived at Wellington, they were 6–8 in. high… Immediately following the main shock, there were more than a hundred aftershocks. Further news is awaited.
From *Nature* 29 November 1952.