Foreign Direct Investment: Does It Threaten the United States?

Is the bottom line that there is no reason whatsoever for concern about foreign ownership of U.S. economic activities? The answer is "no." There is a level of foreign ownership above which few Americans would feel comfortable, where indeed "economic sovereignty" would become a real issue. There are specific activities which for defense reasons should be maintained under domestic ownership.

But whatever the level above which overall foreign ownership should not rise, actual levels of such ownership are surely now much below this threshold. Will FDI in the United States grow at a rate such that the threshold will soon be breached? Prediction is a risky business, but the best guess is "no." Flows of FDI into the United States have declined sharply from the high levels of the late 1980s, and earlier experiences of other advanced nations with surges of inward FDI (for example, Canada and the United Kingdom) suggest that these do not last forever.

Although there are some activities that should not be under foreign control for defense reasons, these are likely to be rather small in number. The United States has adequate laws and policies to deal with these cases. In fact, the danger is not so much that the U.S. government will fail to keep activities out of foreign control that should be retained under domestic ownership, but rather that the government's authority could be used overzealously so as to keep out of the nation activities that should be allowed in.

Some FDI might cause problems in the domain of competition (that is, FDI might result in highly oligopolistic global industries) and, although unilateral application of antitrust law might be one remedy, a more international approach to the regulation of competition is likely to be one agenda for future discussion among nations.

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Population Genetics in Forensic DNA Typing

R. C. LEWONTIN AND DANIEL L. HARTL

Variable number of tandem repeat (VNTR) sequences are used to link defendants with crimes by matching DNA patterns. The probative value of a match is often calculated by multiplying together the estimated frequencies with which each particular VNTR pattern occurs in a reference database. However, this method is liable to potentially serious errors because ethnic subgroups within major racial categories exhibit genetic differences that are maintained by endogamy. The multiplication procedure currently in use can be made scientifically valid only by extensive sampling of VNTR frequency distributions in a variety of ethnic groups, similar to the ethnic studies of various blood groups done in the past. Alternative approaches for dealing with subpopulation heterogeneity are discussed.

FORENSIC SCIENTISTS ARE CONSTANTLY SEARCHING FOR BIOlogical characteristics that are so variable among individuals that an observed match found in material left at the scene of the crime could be taken as conclusive proof linking a suspect with the crime. Fingerprints are the most famous and widely used example (*1*). However, the circumstances under which fingerprints are left and recovered in good condition are limited, so recourse is often made to other physical remains of a crime, like blood type or hair form. These properties, far from being unique, only narrow down the identification to a group, and sometimes a very large group.

With the growth of DNA technology has come convincing evidence that each individual's DNA sequence is unique (*2*). Turning this theoretical principle into a reliable practical tool is the goal of forensic scientists. So far, the approach has been to try to find short stretches of DNA that differ from one individual to the next in ways that can be determined rapidly with high reliability and minimal cost by relatively inexperienced technicians using simple techniques. One form of DNA typing that has recently come into widespread forensic use is the variable number of tandem repeats, or VNTR (*3*). VNTRs are stretches of DNA in which a short nucleotide sequence is repeated tandemly 20 to 100 times. Different VNTR "alleles" are composed of different numbers of repeats, and

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the VNTR alleles can be visualized by DNA hybridization with suitable probes. Typical VNTRs have many different diploid genotypes, most in relatively low frequencies. By combining a number of VNTR systems from different places in the genome, each recognized by a different probe, any individual could, in principle, be characterized uniquely in terms of his or her multilocus VNTR genotype. Because absolute certainty in the identification is not achievable in practice, the next level is to claim virtual certainty by appealing to small probabilities, and examples of calculated match probabilities as small as 1 in 738,000,000,000,000 (based on four loci) and 1 in 450,000,000 (based on two loci and a database of 500 individuals) have been cited (*4, 5*).

The VNTR method is attractive for forensics because sufficient quantities of DNA are often recoverable from dried blood spots, semen samples, or hair follicles (*6*). Even more minute quantities of DNA can be analyzed if the target sequences are amplified prior to analysis by the polymerase chain reaction. Consequently, DNA typing has been introduced in scores of prosecutions in recent years, especially in murders and rapes, as well as in paternity disputes. In 1989, the Federal Bureau of Investigation established its own DNA typing facility, several private companies have been formed for DNA typing on contract from various law enforcement agencies, and the Department of Justice has funded several academic research programs for work on VNTR typing. Advocates of the VNTR method sometimes use the term "DNA fingerprinting," but the DNA profile of an individual, as determined by current forensic procedures using (at most) a handful of VNTRs, has far less information content than a fingerprint.

VNTR profiles are subject to technical problems relating to the discrimination of alleles and repeatability of the tests themselves. Alleles that differ by only a few repeats do not separate enough in gels to be reliably distinguished. Consequently, the complete array of VNTR alleles does not form a series of discrete character states, but a quasi-continuous array of phenotypes, like height or weight. Thus, it is necessary to set up an arbitrary set of phenotypic boundaries for band size, which delimit so-called "bins" (7). Two bands assigned to the same bin may, in fact, contain different numbers of repeats. In addition, there is variation from one DNA preparation to the next, and from gel to gel, in the rate of migration of identical DNA fragments (*8*).

Appropriately carried out and correctly interpreted, DNA typing is possibly the most powerful innovation in forensics since the development of fingerprinting in the last part of the 19th century. Although discussions of statistics in DNA typing necessarily focus on the interpretation of matching band patterns, it is important to note that DNA mismatches are equally important because they are exclusionary. Indeed, barring technical errors resulting in false negatives, DNA mismatches are definitive with no need to invoke statistics. In the actual experience of various DNA typing laboratories dealing with specimens in criminal cases, as many as 37% of the cases are exclusions and approximately 20 to 25% cannot be resolved by DNA typing because of an insufficient quantity of DNA or other technical reasons (*9*).

Our concern is with the 40 to 50% of criminal cases in which a suspect's VNTR profile does match that of a forensic sample. The question is whether a valid and reliable estimate of the probability of matching between "random" individuals can be obtained with the use of the current method of multiplying together the estimated frequencies with which each of the individual VNTR pattern occurs in a reference database.

The Problem

The problem of estimating the probability of a match between two randomly chosen individuals raises the following questions:

1) What is the reference population from which the randomly chosen individual is to be taken?

2) How are data from separate VNTR loci to be combined so as to give an overall probability of finding a given DNA profile that includes several different loci?

With regard to the first question, reference data sets have been established for "Caucasians" and "blacks" consisting of frequencies of alternative VNTR alleles for a number of VNTR loci in several samples (7). North American "Caucasians" and "blacks" are each claimed to constitute a homogeneous population undergoing random mating within itself, so that reliable probability statements can be made based on the reference samples (7).

With regard to the second question, the assertion is that population frequencies of DNA types across multiple VNTR loci can be estimated reliably by multiplying the frequencies for each of the VNTRs separately (7). The rationale for this assertion is the assumption that "Caucasians" and "blacks" are random mating groups within themselves and that, because different VNTR loci are located on different chromosomes, they must assort at random and be independent in a statistical sense. In the language of population genetics, the assumption is that the loci are in "linkage equilibrium" (also called "gametic phase balance").

Both of these claims are based on misinterpretations of population genetics theory. More importantly, they ignore a considerable body of evidence indicating genetic substructure within what are called the "Caucasian," "black," and "Hispanic" populations. The census populations designated "Caucasian," "black," and "Hispanic" are actually each made up of multiple subpopulations that are genetically diverse. Consequently, with currently available data, the current method of estimating the probability of a match by multiplying together the frequencies with which each of the individual VNTR pattern occurs in a reference database is unjustified. Furthermore, the magnitude and direction of the error depends on the particular VNTR locus, the bands observed, and the reference database. Hence, it cannot be ascertained whether the estimates as currently calculated are biased for or against any particular defendant. On the other hand, although the current method is flawed, it is not irretrievable, and suitable data could be gathered that would allow acceptable probability estimates to be made. Perhaps a better solution would be to abandon the current method altogether and replace it with one or more of the alternative approaches that are discussed below.

Some Theoretical Misunderstandings

The principles of population genetics that are pertinent to interpreting DNA types are simple but prone to being misunderstood.

Random mating. The term "random mating" has two very different meanings.

First, the narrow sense of random mating, with respect to any physical or genetic characteristic, means that the characteristic is not a direct determinant of choice of mate. For example, people normally do not consider ABO blood type in choosing their mates, and so in this sense (and only in this sense) do people mate "at random" with respect to ABO blood type. The narrow sense of random mating typically applies to blood groups, VNTRs, and other biochemical marker genes that do not have a direct effect on people's appearance, odor, behavior, or other factors that directly affect choice of mate.

Second, the broad sense of random mating means that individuals choose their mates without regard to religion, ethnicity, geography, and so on. However, human populations typically form endogamous groups based on precisely these characteristics, and individuals

tend to marry within their group. If the endogamous groups within a larger population differ from each other genetically, for any reason, then, from the perspective of the population as a whole, there is nonrandom mating among the genotypes, even though no individual selects a partner based on his or her genes. From the standpoint of the entire census population, when people choose their mates endogamously, they are unconsciously making a choice among blood groups and other traits correlated with ethnicity.

Linkage disequilibrium (gametic phase imbalance). When populations are first established by admixture, they may have linkage disequilibrium between different loci, even between loci that are on different chromosomes (like many VNTRs). It is sometimes asserted that a single generation of random mating will eliminate any linkage disequilibrium, but the elementary principles of population genetics show that this is untrue. If a population is undergoing complete random mating (in both of the above senses), and if there is free recombination between the loci, then, in each generation, the remaining amount of linkage disequilibrium is reduced by half, so that in successive generations the amount of linkage disequilibrium equals one-half, one-quarter, one-eighth, and so on, of the original amount. The reduction in linkage disequilibrium depends not only on the recombination frequency but also on the frequency of double heterozygotes, and if the population is not panmictic, but contains endogamous subgroups, then the linkage disequilibrium decreases more slowly, in proportion to the amount of endogamy, because the frequency of double heterozygotes is reduced (*10*).

Hardy-Weinberg equilibrium. Much courtroom discussion (*11*) and scientific effort (*7, 12*) relative to DNA typing has focused on statistical tests of Hardy-Weinberg equilibrium (HWE) in human populations. The emphasis on HWE is based on the proposition that population substructure (for example, endogamy) will result in deviations from HWE (*13*). As a practical matter, however, statistical tests for HWE are virtually useless as indicators of population substructure because, even for large genetic differences between subgroups, the resulting deviations from HWE are generally so small as to be undetectable by statistical tests. Therefore, the lack of statistically significant deviations from HWE does not imply the absence of substructure. Statistical tests for HWE are so lacking in power that they are probably the worst way to look for genetic differentiation between subgroups in a population. The proper approach is the straightforward one of sampling the individual subgroups and examining the differences in the genotype frequencies among them (*14*).

Genetic Substructure in Actual Populations

For DNA typing, the main issue is whether genetic substructure within various human populations is so great as to nullify the estimated probabilities of DNA profiles. The specific questions are, first, whether it is legitimate to use a single pooled "Caucasian" sample to estimate allele frequencies of individual VNTRs, and, secondly, whether it is legitimate to estimate the probabilities of multilocus genotypes by multiplying frequencies of the separate VNTRs. The issues can be addressed only in part with data from VNTRs, because there are few relevant studies of population substructure that use VNTRs. However, genetic substructure can be inferred from data on immigration and marriage patterns as well as from a large number of studies of blood-group genes and enzyme-coding genes.

Genetic substructure within conglomerate populations like the "Caucasians" of North America will occur under the following conditions: (i) If there was genetic differentiation among the ancestral populations that contributed immigrants to the conglomerate population; (ii) if only a few generations have passed since the mixing; or (iii) if there is pronounced endogamy, with the effect that descendants of the original immigrants tend to marry each other rather than forming a large, panmictic, biological "melting pot."

All three of these conditions do occur within the "Caucasian," "black," and "Hispanic" census populations of North America. Each group consists of genetically differentiated subgroups that must be specified separately whenever a probability calculation is to be made that pertains to a member of any of the constituent subgroups.

Caucasians

Genetic differentiation among ancestral populations. Among genes that are polymorphic in European national or ethnic groups, the magnitude of the differences in allele frequency among subpopulations differs from one gene to the next (*15, 16*). Some genes, such as those determining the Duffy, P, and Xm factors, show little variation in frequency from region to region. For other genes there is a great deal of variation. For example, there are striking geographical clines of allele frequency across Europe for the ABO blood groups: the frequency of the B allele is 5 to 10% in Britain and Ireland, increases across Eastern Europe, and reaches 25 to 30% in the Soviet Union; the frequency of the O allele is 70 to 80% in Sardinians, Irish, and Scottish populations but lower in Eastern European populations. These clines reflect the migrations and political history of Europe over the last few thousand years. The blood group frequencies in southern Spain are similar to those in the Near East and North Africa, reflecting six centuries of Arab rule in the southern Iberian peninsula. Although the last Muslim kingdom was expelled from Spain in 1492, the genetic legacy lingers after 500 years.

Pronounced genetic differentiation also occurs in the blood group Le(a- b-), which has frequencies of 3.8% in Scots, 28.7% in Swedes, and 32.4% in Greeks; Kell(+) varies from 3% in Italians to 11% in Poles; and Lu(a+) varies from 0.86% in Welsh to 8.5% in Irish to 10% in Poles (*15*). Of special interest is the array of *Rh* alleles, which is analogous to most VNTR loci in having a large number of alleles with different frequencies. For some *Rh* alleles there is little or no differentiation among subpopulations (for example, the frequency of *cde* is 30 to 40% in almost all samples), whereas other alleles show relatively large variation (for example, the frequency of *CDE* varies by more than a factor of ten among samples from different regions in Spain, and that of *cDe* varies from 0.65% in Italians to 4.7% in Poles).

The blood group genes are typical, not rare exceptions or "outriders" (*17*) chosen simply to make a point. Lewontin (*18*) studied genetic differentiation of human populations using a sample of 17 genes chosen because they were highly polymorphic and sampled among many diverse human populations. The result of this analysis is that most human genetic diversity reflects differences among individuals within local populations (85.4% when averaged over all 17 genes). The remaining 14.6% of human genetic diversity broke down as follows: 8.3% among local ethnic and linguistic subpopulations within races, and 6.3% between the major races. That is, for these genes, there is, on average, one-third more genetic variation among Irish, Spanish, Italians, Slavs, Swedes, and other subpopulations, than there is, on the average, between Europeans, Asians, Africans, Amerinds, and Oceanians.

Recentness of origin. Although it is commonly assumed that the United States was populated by immigrants largely in the 19th century, the greatest immigration, almost entirely from Europe, began about 1905 and continued until curtailed by the Immigration Restriction Act of 1924. The Census Bureau's historical statistics of the United States indicates an average of nearly a million immigrants per year during this period, during which the total population grew

from 85 to 110 million. By 1920, in a total "Caucasian" population of 94.8 million Americans, 13.8 million (14.5%) were foreign born themselves, and a further 22.7 million (24%) had foreign-born parentage. Even today, the typical adult "Caucasian" in the United States is the grandchild of immigrants. For "Hispanics" the situation is at least one generation delayed (counting Puerto Ricans as immigrants). The key point for DNA typing is that there has been very little time for mixing of genes from diverse populations of origin.

Marriage patterns. The notion of an American "melting pot" is true for some aspects of culture, but certainly not for marriage, which is strongly affected by religion and ethnicity (*19–23*). Because most adult Americans are the children of marriages contracted 30 to 50 years ago, the earlier data are relevant. Kennedy's New Haven study (*20, 21*) showed levels of endogamy by ethnicity in excess of 80%. As urbanization occurred, the level of endogamy decreased between 1870 and 1900 for some groups, such as Germans, British, and Irish, but not for other groups, such as Jews and Italians. Data from Minnesota also showed very high endogamy by national origin (*19*). By the period 1930 to 1940 the level of endogamy by ethnicity had about stabilized, but there has been extremely high endogamy by religion during all periods (*20*).

In addition to ethnicity and religion, another element in endogamy is geographical distance. Indeed, the so-called propinquity model of marriage is a standard in demography and sociology. A classic study (*24*) showed that a third of marriages are contracted between persons born less than 10 miles apart, supporting the truism of sociology that Americans tend to marry the girl or boy next door. The net effect of propinquity, ethnic preferences, and religious custom is to produce a population that is highly biologically subdivided in regard to mating.

Consequences of genetic substructure. We have seen that "Caucasian" Americans are derived from genetically diverse European subgroups that migrated to North America only in recent generations and that have tended to maintain their ethnic and religious separateness in marriage. The consequences are twofold. First, there exists no single homogeneous reference group to which all individuals can be referred for estimating probabilities of a random match of DNA type. Rather, each particular individual may require a different reference group composed of appropriate ethnic or geographic subpopulations.

The second consequence of population substructure is that the multiplication rule for calculating probabilities across multiple VNTR loci does not apply. If subpopulations differ in their allele frequencies at two different loci, then these loci will not be in linkage equilibrium in the population as a whole, and separate multiplications must be carried out within each group to get a reliable estimate of the probabilities.

Actual data on blood groups from European populations illustrate the effects of population subdivision on the probabilities of multilocus genotypes. We have not chosen the data so as to produce the maximum possible discrepancy between ethnic groups, nor to demonstrate any particular difference between the groups, but merely to show that large differences in the probabilities of multilocus genotypes have already been seen in some commonly studied genes. In our example, Italians and Poles were chosen because they represent large immigrant populations in the United States whose descendants reside, for the most part, in the same urban areas and so are represented in the same pools of potential defendants or victims. Because the majority of forensic cases involve two-banded patterns, we consider heterozygotes *A/B* for the ABO locus, heterozygotes *K/k* for the Kell locus, and *Cde/cDe* for the Rh locus. This last choice is dictated by the similarity of frequencies of these alleles to the majority of VNTR bin frequencies, which typically range from 1 to 4%. The allele frequencies and their ratios for the two populations are shown in Table 1.

Table 1. Allele (*15*) and genotype frequencies for selected blood group genes in an Italian and a Polish population. The multilocus genotype probabilities have been calculated under the assumption of HWE within each population.

Population	*cDe*	*Cde*	*K*	*k*	*A*	*B*	Multilocus genotype probability
Poles	0.047	0.044	0.058	0.942	0.37	0.22	7.4×10^{-5}
Italians	0.0065	0.015	0.015	0.985	0.37	0.07	3.0×10^{-7}
Ratio	7.23	2.93	3.87	0.96	1.00	3.14	247

The expected ratio of genotype probabilities for the two populations is then found by multiplying $7.23 \times 2.93 \times 3.87 \times 0.96 \times 1.00 \times 3.14 = 247$. That is, Poles are about 250 times more likely to match for these genotypes than are Italians. The implication for DNA typing is that American ethnic groups may have substantial differences in the frequencies of multilocus genotypes. Therefore, it is inappropriate to use a general multiplication rule and an arbitrary "Caucasian" database to calculate the probability of a multilocus VNTR match. Nevertheless, if the only choice were between Italians and Poles, the value 7.4×10^{-5}, or one in 13,590, would be conservative. This observation suggests a way around the problem, which is one of the alternatives discussed below.

Table 2. Frequencies of selected bins for VNTR probe D2S44 in a French and Israeli sample. Data are from (*11*). The samples sizes are 346 (French) and 236 (Israeli).

Bin number	France	Israel	Ratio
1	0.032	0	Infinity
6	0	0.042	zero
8	0.058	0.017	3.4:1
12	0.095	0.034	2.8:1
21	0.009	0.042	1:4.7

In comparing gene or genotype frequencies in different subgroups, the ratio of frequencies is the important quantity, not the absolute frequencies. In particular, for alleles at low frequency, including nearly all VNTR alleles, what appear superficially to be small differences in absolute frequencies may be very large in terms of relative frequencies. A frequency difference of 1% versus 3% may seem trivial, but in determining the probabilities of matching DNA types, it introduces an error of a factor of 3 in the estimated probability of a match for the locus in question. This point is illustrated in Table 2 with data for VNTR probe D2S44 in samples from France and Israel. The differences do not result simply from chance variations in small samples (a *G* test on the entire distribution gives $P < 10^{-6}$), and so the differences between the French and Israeli populations are real.

Bins that are well represented in one population sample but nearly absent in another are a frequent occurrence among loci with large numbers of alleles. These bins pose a particularly difficult problem for the forensic use of VNTRs because if the wrong ethnic group is used as the reference population, then a very low probability, even zero, may be assigned to a particular VNTR type, when the true probability may actually be relatively high in the proper ethnic group. Therefore, vague claims of the similarity between population samples based on a general similarity in the "shape" of the VNTR distributions (or any other distributions in which there are many classes) are irrelevant, since it is the ratios of the classes that are critical (*25*).

Other Census Groups

Existing VNTR data indicate that the allele frequencies in non-Caucasian groups differ very substantially from each other and from those in Caucasians (*26, 27*). Furthermore, population substructure also occurs within the census populations denoted as "blacks," "Hispanics," and "native Americans."

"*Blacks*." No reliable historical data exist concerning the diverse origins of the African slaves brought to North America. American blacks in different localities have various amounts of European and American Indian ancestry acquired since their introduction into North America. Several alleles are known in Africans that are absent in Europeans and vice versa. For example, the *Fy-b* allele is absent in Africans but has an average frequency of about 45% in white North Americans and even greater in American Indians. Using the frequency of this allele in Americans classified as "black," one can estimate the proportion of "white" (actually, an unknown mixture of Caucasian and American Indian) ancestry in the population. This calculation suggests that blacks from South Carolina have 3.7% "white" ancestry, whereas those from Detroit have 26% "white" ancestry. These sorts of data do not exist for VNTRs. However, because many genes differ markedly in frequency between Africans and Europeans, reliable probabilities for black victims or defendants cannot be estimated without use of a reference population that is at least geographically relevant and that takes family history into account.

"*Hispanics*." This heterogeneous assemblage is perhaps the worst case for calculating reliable probabilities. The census designation "Hispanic" is a biological hodgepodge. It includes people of Mexican, Puerto Rican, Guatemalan, Cuban, Spanish, and other ancestries. But many Guatemalans are not "Hispanic" at all; they are almost all pure Indian. Mexicans, too, have a large and variable component of Indian ancestry. On the other hand, Puerto Ricans and Cubans have little or no Indian ancestry but do have considerable African ancestry. Another complication occurs in Spaniards and Argentinians, who have virtually no Indian or black African ancestry. American Indians have some gene frequencies that depart widely from those of other groups: high frequencies are found for blood group O (many populations are entirely O), blood group M (ranging from 75 to 90%); and some of the Rh types (for example, *cDE*). Moreover, American Indians differ markedly in allele frequencies of VNTR and other DNA markers. For example, the Karitiana of Brazil are virtually fixed for alleles of VNTR D14S1 in the size range 3 to 4 kilobases, whereas the Surai of Brazil have 62% heterozygosity for this locus (*11, 27*); and certain three-locus VNTR genotypes differ in frequency by a factor of more than 500 in these populations, even though they are separated by only 420 kilometers (*11*). Because of the extreme heterogeneity among "Hispanics" and among "native Americans," it is doubtful whether any reference population could be defined that would be reliable in a forensic context.

What Is to Be Done?

Both the theory of population genetics and the available data imply that the probability of a random match of a given VNTR phenotype cannot be estimated reliably for "Caucasians," probably not for "blacks," and certainly not for "Hispanics," if the present method of calculation and the databases presently available are used. As currently calculated, the estimates may be in error, possibly by two or more orders of magnitude. The error may be in favor of the defendant, or against the defendant, and the magnitude and direction of the error is impossible to evaluate in any particular case without additional data.

The main problems with the current calculations are twofold. First, the probability estimates are unduly influenced by VNTR patterns that are uncommon in the reference database, and it is precisely the uncommon VNTR patterns whose frequencies are most difficult to estimate accurately. Moreover, one consequence of multiplying frequencies across loci is that the potential errors at each locus also multiply, and by the time three or four successive multiplications have been carried out, the accumulated error can easily be two or more orders of magnitude (for example, Table 1). Second, the current method often confronts the very real dilemma of not being able to specify a suitable reference database.

But the current method is only one of several possibilities, and a number of alternative approaches alleviate (if not eliminate) most of the problems with the current method. A few of the alternatives are listed below, more in order of simplicity than in order of preference. None of the alternatives take into account the probability of a false match through laboratory artifact or error. The rate of false positives defines a practical lower bound on the probability of a match, and probability estimates based on population data that are smaller than the false-positive rate should be disregarded. Hence, probability estimates like 1 in 738,000,000,000,000, however, they are calculated, are terribly misleading because the rate of laboratory error is not taken into account.

1) *Don't multiply*. As the estimated probability of a match, use the frequency of the multilocus VNTR in an appropriate reference database. Multilocus VNTR patterns containing several rare alleles will, in many cases, not be represented in the databases, and in such a case the estimated probability is estimated as less than $1/x$, where x is the total number of individuals in the database. This method makes use of admittedly imperfect databases for each major racial group, but it appears to be conservative in that the smallest estimated probability of a multilocus match is the reciprocal of the database size, which is unlikely to exceed a few thousand.

2) *Ethnic ceilings*. This method makes use of a set of databases from different ethnic subpopulations within the major racial groups. For each locus, the estimated frequency of the VNTR phenotype is taken as the maximum value observed among the relevant ethnic subpopulations, and these locus-specific estimates are multiplied together to obtain the composite estimate of the probability of the multilocus match. Lander (*5*) has pointed out that this approach should be reasonably robust even if the defendant's particular ethnic composition is not represented in the databases, because the particular ethnic subpopulations in the database could be chosen to span most of the range of variation in VNTR phenotype frequencies. Furthermore, there may be VNTR loci that differ little among ethnic subpopulations, and these could be used without further qualification (*28*).

One useful feature of this method is that it does use the frequencies of rare VNTR phenotypes if they are rare in all the ethnic subpopulations, and thus the multilocus probabilities will often be much smaller than in the more conservative method discussed earlier. Moreover, the trade-off for possibly obtaining much smaller composite frequencies is the relatively modest one of documenting the range of variation in the VNTR phenotype frequencies among ethnic subpopulations within the major racial groups.

3) *Fix the current method*. This approach is the most difficult to implement correctly but will usually yield the smallest estimated probabilities. It uses the current method of multiplication across VNTR loci, but in order to be scientifically reliable, the databases must be expanded to include detailed knowledge of the VNTR frequency distributions in a wide variety of ethnic subgroups that are likely to be relevant in forensic applications. Some data of this sort has begun to appear for Amerindians (*27*), Hispanics (*29*), and American blacks (*30*). Not surprisingly, differences that are highly statistically significant are found among subgroups, confirming the

current understanding of human population substructure and genetic differentiation inferred from extensive anthropological sampling of blood groups and enzymes.

All of these approaches, even the first, require information about actual allele frequency distributions in a wide variety of ethnic subgroups that are likely to be relevant in forensic applications. Without the type of subpopulation studies already carried out for blood groups and enzymes, estimates of the probability of a matching DNA profile based on VNTR data, as currently calculated, are unjustified and generally unreliable.

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10. For example, if there is free recombination and 50% endogamy, then the proportion of the initial linkage disequilibrium that remains in successive generations follows the series 3/4, 9/16, 27/64, and so on; if the population had 80% endogamy, 2/3 of the original linkage disequilibrium would still be present after four generations.
11. *U.S. v. Yee*, 129 Federal Rules Decisions 629 (Northern District of Ohio) (1990).
12. R. Chakraborty and S. P. Daiger, *Hum. Biol.* **63**, 571 (1991).
13. R. Chakraborty, *Am. J. Human Genet.* **49**, 895 (1991).
14. To illustrate with a specific example, suppose a census population consists of a 9:1 mixture of two subpopulations with frequencies of an allele A of 0.5 and 0.9, respectively, and that each subpopulation mates randomly within itself. Then the excess of homozygotes in the census population is only 2.88% as compared with HWE, which would require a sample size of 1160 or larger to have a better than 50% chance of being detected by the conventional chi-square test. In contrast, a sample of only 11 individuals from each subpopulation would ensure a 50% chance of obtaining statistical significance in a chi-square test of the difference between the allele frequencies themselves.
15. A. E. Mourant, *The Distribution of Human Blood Groups* (Blackwell, Oxford, 1954).
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22. S. Lieberson, *Ethnic Patterns in American Cities* (Free Press, New York, 1962).
23. C. Peach, *Ethnic Segregation in Cities* (Univ. of Georgia Press, Athens, GA, 1981).
24. J. N. Spuhler and P. J. Clark, *Human Biol.* **33**, 223 (1961).
25. There is also the view that, because the true probability of a match at multiple VNTR bands will often be small, any estimate that is small will serve for courtroom purposes, even if the theoretical calculations are unjustified or if the reference database is faulty (*11*). The mistake here is to suppose that the true probability of a match is small when, in fact, it is unknown.
26. I. Balazs, *et al.*, *Am. J. Hum. Genet.* **44**, 182 (1989).
27. J. R. Kidd *et al.*, *Human Biol.* (1991).
28. On the other hand, it is unlikely that such loci will be found among the highly variable, and therefore, most informative, loci. Differentiation among subgroups is expected to be particularly pronounced for loci with large numbers of alleles, each in low frequency, especially in species like humans whose evolutionary history has mostly occurred in small, isolated local populations.
29. B. Budowle *et al.*, *Crim Lab. Digest* **18**, 9 (1991).
30. R. T. Acton *et al.*, in *Proceedings of the International Symposium on Human Identification 1989: Data Acquisition and Statistical Analysis for DNA Typing Laboratories* (Promega Corporation, Madison, WI, 1990), pp. 5–20.

Oscillatory Kinetics and Spatio-Temporal Self-Organization in Reactions at Solid Surfaces

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Chemical reactions far from equilibrium on solid surfaces may exhibit typical phenomena of nonlinear dynamics, as exemplified by the catalytic oxidation of carbon monoxide on a platinum(110) single-crystal surface. Depending on the external parameters (temperature and partial pressures of the reactants), the temporal variation of the reaction rate may become oscillatory or even chaotic. In a parallel way, the concentration distributions of the adsorbed species on the surface form spatio-temporal patterns including propagating and standing waves, rotating spirals, as well as irregular and rapidly changing structures denoted "chemical turbulence."

IF A CHEMICAL REACTION IS OPERATED UNDER FLOW CONDITIONS with fixed external parameters, it will usually also exhibit a constant, steady-state rate of product formation. In certain cases, however, the response of the system may vary periodically or aperiodically with time. The most famous example is offered by the Belousov-Zhabotinsky (BZ) reaction in well-stirred homogeneous solution (*1*), in which periodic color changes reflect varying composition. Apart from other homogeneous reactions (*2*), certain heterogeneous processes occurring at gas-solid or liquid-solid interfaces were also found to exhibit such phenomena of temporal self-organization. These comprise electrochemical systems (*3*) as well as heterogeneously catalyzed reactions, either occurring with "real" catalysts near atmospheric pressure (*4*) or under ultrahigh vacuum conditions with well-defined single-crystal surfaces (*5*).

As an example (*6*), the variation of the potential U can be shown

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