Nanoelectromechanical systems

Nanodevice motion at microwave frequencies

It has been almost forgotten that the first computers envisaged by Charles Babbage in the early 1800s were mechanical[1,2] and not electronic, but the development of high-frequency nanoelectromechanical systems is now promising a range of new applications[3], including sensitive mechanical charge detectors[4] and mechanical devices for high-frequency signal processing[5], biological imaging[6] and quantum measurement[7–9]. Here we describe the construction of nanodevices that will operate with fundamental frequencies in the previously inaccessible microwave range (greater than 1 gigahertz). This achievement represents a significant advance in the quest for extremely high-frequency nanoelectromechanical systems.

Until now, it has not been possible to create mechanical devices that operate at extremely high frequencies, owing to the dual challenge of detecting tiny displacements (on the scale of femtometres) at microwave frequencies[1,3]. The characteristic frequency of nanoelectromechanical systems (NEMS) scales upwards with decreasing size, but their displacement (when operating linearly) and their electromechanical impedance both simultaneously scale downwards.

Two advances have been crucial to breaking the 1-GHz barrier in NEMS: the use of silicon carbide epilayers[10], which are of comparable density but are significantly stiffer than the usual silicon[11,12], and which allow higher frequencies to be attained for structures of similar geometry; and the development of balanced, high-frequency displacement transducers, which enable the ubiquitous passive embedding impedances that arise from electrical connections to the macroworld to be nulled[13] (if uncontrolled, these parasitic impedances overwhelm the electromechanical impedance of interest — the 'signal' — in ultrasmall NEMS).

We used 3C–SiC films that were grown hetero-epitaxially at atmospheric pressure by chemical-vapour deposition in an induction-heated reactor on 100-mm-diameter (100) Si wafers[10]. Device nanofabrication involves both optical and electron-beam lithography to define, respectively, large-area contact pads and submicrometre-scale, thin metallic-film masks with the device geometry. Pattern transfer to the 3C–SiC layer is achieved by an electron cyclotron resonance (ECR) plasma-etch step involving an $NF_3/O_2/Ar$ mixture. The patterned 3C–SiC beams are then suspended above the underlying silicon substrate by using an isotropic NF_3/Ar ECR etch. The metallic mask (30 nm of aluminium, followed by 5 nm of titanium), deposited by e-beam evaporation and patterned by lift-off, remains on the beams and is used as the electrode for displacement transduction. The devices consist of two nominally identical, doubly clamped beams, roughly 1.1 μm long, 120 nm wide and 75 nm thick.

Each doubly clamped beam pair is positioned perpendicular to a strong magnetic field (3–8 tesla) *in vacuo* within a liquid-helium cryostat. Balanced magnetomotive detection is used[13]; when the driving frequency matches the fundamental frequency of the in-plane flexural mode for one of the beams, there is resonant enhancement of the induced electromotive force. This response is pre-amplified and characterized by a microwave-network analyser.

Fundamental mechanical resonances are detected at 1.014 GHz and 1.029 GHz for the two beams (Fig. 1). So far, quality factors attained above 1 GHz (about 500) are substantially lower than observed for NEMS in roughly the 100-MHz range (about 10^4). Having ruled out factors such as electrical damping, we are investigating whether this stems from roughness in the initial SiC epilayers, and how such sources of acoustic loss in microwave NEMS can be minimized. Nonetheless, this step into the previously inaccessible domain of microwave-frequency mechanical excitations constitutes a milestone along the path to the many new applications offered by nanomechanical systems.

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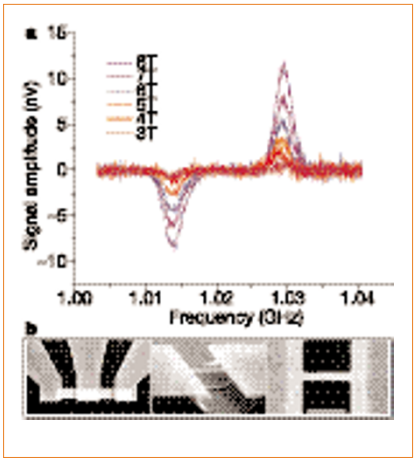

Figure 1 Microwave-frequency nanomechanical devices. **a,** Fundamental flexural-mode resonant mechanical response at 1.014 and 1.029 GHz, detected at about 4.2 K from a pair of doubly clamped silicon carbide beams as a function of applied magnetic field (3–8 tesla). These devices are electrically connected within a balanced magnetomotive detection scheme[12]; each distinct resonance corresponds to excitation of one of the beams within the device. **b,** Scanning electron micrographs of a similar (slightly larger) pair of devices, with magnified views of a single resonant element. Scale bar, bottom right, 1 μm.

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Competing financial interests: declared none.

COMMUNICATIONS ARISING

Genomic function

Rate of evolution and gene dispensability

Whether more dispensable genes evolve faster than less dispensable ones[1] is a contentious issue[2–4]. Comparing yeast and worm genes, Hirsh and Fraser[3] observe a gradual tendency for less dispensable genes (those that reduce the growth rate of yeast when knocked out) to have lower rates of protein evolution. Here we repeat their analysis using larger data sets and find no evidence that dispensability explains the variation in rates of protein evolution. Although Hirsh and Fraser provide a model to show why their result is to be expected, our analysis suggests that their model, which assumes among other things that no substitution is advantageous, cannot be generally applied.

To estimate the rate of evolution, Hirsh and Fraser used orthologues identified in the worm *Caenorhabditis elegans*. But using so distant a relative of the yeast *Saccharomyces cerevisiae* may have pitfalls. We have therefore repeated the analysis using *C. elegans* and three other closer relatives of *S. cerevisiae* (*S. bayanus*, *Candida albicans* and *Schizosaccharomyces pombe*). Unlike *Caenorhabditis*, for which the most recent common ancestor with yeast existed between 1.0 billion and 1.6 billion years ago, these three species are separated from *S. cerevisiae* by about 10 million, 140–310 million and 330–440 million years, respectively. New fitness data[5] enable complete genomes to be analysed using samples that

are, on average, an order of magnitude larger than those used by Hirsh and Fraser.

Orthologues of *S. cerevisiae* proteins in each of the four genomes were identified by reciprocal pairwise searches[6]. Protein sequences were aligned using CLUSTAL-W software with the default settings; only those alignments with less than 20% gap were retained. Protein evolutionary distances were calculated by using a maximum-likelihood method[7] and Dayhoff's substitution matrix (using different substitution matrices or allowing for rate variation among sites did not alter our results). Whole-genome transcription data[8] gave a measure of gene expression (using codon-adaptation indexes as estimates of gene-expression rates[9] gives results that are qualitatively similar).

The correlation between dispensability (that is, the effect on fitness of knocking out the gene) and the rate of evolution for each of the analyses suggests, at most, only a very weak effect (Fig. 1). Although, in Hirsh and Fraser's original analysis, gene dispensability accounts for 8.5% (or 20% under ranked correlation) of the variation in rate of protein evolution (A. Hirsh, personal communication), in the larger data sets this is reduced by roughly an order of magnitude (Fig. 1); Hirsh and Fraser's repeat worm analysis showed a similar reduction[10]. This indicates that the high r^2 value obtained in the authors' original analysis is largely an artefact due to their limited sample size.

Likewise, the variation in the correlation coefficients in our four data sets is a result of the different sets of appropriate orthologues used. When the same set of *S. cerevisiae* genes is used for comparison with *C. albicans*, *S. pombe* and *C. elegans*, the correlations are not statistically different and none is significant (results not shown).

The tiny amount of variation that might be explained by dispensability seems to be a weak covariate of expression rate. More dispensable genes tend to be expressed at a lower rate than less dispensable ones ($N = 3{,}783$, Pearson $r_{\log(\text{expression})-\text{fitness}} = 0.191$, $P < 10^{-8}$, Spearman $\rho_{\text{expression}-\text{fitness}} = 0.155$, $P < 10^{-8}$), possibly because these genes have less phenotypic contribution. The rate of expression is a good predictor of the rate of protein evolution[11]. If we control for the covariance with expression rates, we do not see any correlation between fitness and rate of protein evolution ($P > 0.172$ for all comparisons; Fig. 1 legend). However, when we control for the dispensability of genes, we still find that expression rate is a strong predictor (Spearman partial $\rho_{\text{expression}-\text{protein distance}|\text{fitness}} < -0.49$, $P < 10^{-7}$ for all comparisons).

We therefore see no evidence that dispensability is a relevant variable in understanding the rates of protein evolution. More generally, claims that any given variable is important in predicting rates of protein evolution should control for what seems to be a good predictor — the rate of expression. Neither gene dispensability nor recombination rate[6] seems to be as important a variable after such control.

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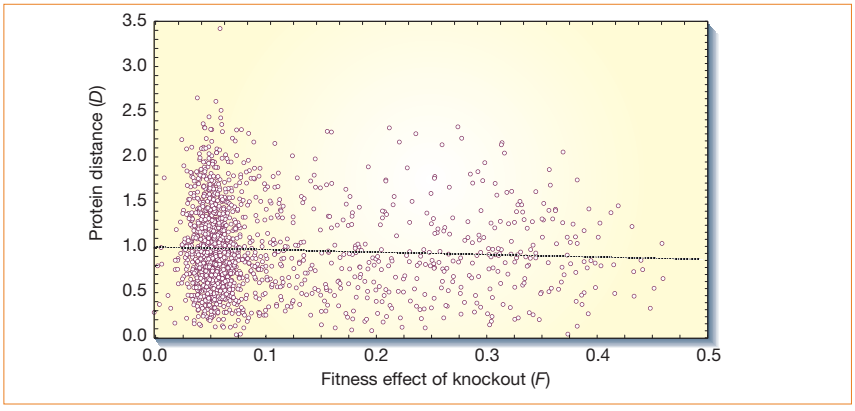

Figure 1 Relationship between the rate of protein evolution (protein distance, *D*) and the fitness effect of knockout (*F*, 1 − dispensability) for genes in a comparison involving a range of yeast species ($N = 1{,}660$, Pearson $r^2_{FD} = 0.00289$, $P = 0.028$, Spearman rank $\rho^2_{FD} = 0.00515$, $P = 0.0034$). Graph shows the result of the comparison of *Saccharomyces cerevisiae* and *Candida albicans*; dotted line indicates the best-fit linear regression. After controlling for expression rate (*E*), the correlation disappears (for *C. albicans*: $N = 1{,}554$, Pearson partial $r_{FD|\log E} = 0.003$, $P = 0.9$, Spearman partial rank[12] $\rho_{FD|E} = -0.0343$, $P = 0.172$; for *Schizosaccaromyces pombe*: $N = 1{,}090$, $r_{FD} = -0.103$, $P < 0.001$, $r_{FD|\log E} = -0.015$, $P = 0.619$, $\rho_{FD} = -0.1077$, $P < 0.001$, $\rho_{FD|E} = -0.0249$, $P = 0.41$; for *Caenorhabditis elegans*: $N = 490$, $r_{FD} = -0.122$, $P = 0.007$, $r_{FD|\log E} = 0.0134$, $P = 0.768$, $\rho_{FD} = -0.171$, $P < 0.001$, $\rho_{FD|E} = -0.0449$, $P = 0.317$; for *Saccharomyces bayanus*: $N = 154$, $r_{FD} = -0.151$, $P = 0.061$, $r_{FD|\log E} = -0.0159$, $P = 0.845$, $\rho_{FD} = -0.227$, $P = 0.0047$, $\rho_{FD|E} = -0.0864$, $P = 0.294$). *P* values for Spearman partial-rank correlations were assessed by randomization. Only non-essential genes were studied ($F < 1$), as in ref. 3.

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Hirsh and Fraser reply — The relationship between protein dispensability and rate of evolution that we detected in yeast[1] has since been confirmed among bacteria[2] — as well as in the same data set[3,4] that Pal *et al.* refer to as "new fitness data" and which they re-analyse here using methods that fail to reveal the relationship.

In each of the three studies that demonstrate this association, the correlation was small but highly significant. The interest of the finding was not that it explained a large proportion of the total variance in protein evolutionary rate (it did not), but rather that, despite several obvious sources of noise and error — for example, fitness effects were measured in a single laboratory medium and not in the wild — a statistically significant pattern was detectable, confirming a basic prediction of a widely held model of protein evolution[5]. The question that arises from the comment of Pal *et al.* is therefore whether there is still a significant relationship between dispensability and evolutionary rate when the best available estimates of evolutionary rate, expression level and deletion effect are used.

In a re-analysis that differs from that of Pal *et al.* in several important ways, we still find a highly significant relationship between protein dispensability and evolutionary rate, even when we control for the level of gene expression. Using three complete genomes in the *Saccharomyces* genus, each of which diverged from *S. cerevisiae* less than 10 million years ago, as well as the more distant comparisons used by Pal *et al.* (*S. pombe*, *C. albicans* and *C. elegans*), we estimated the evolutionary rates of *S. cerevisiae* proteins. Pal *et al.* relied exclusively on BLAST to identify putative orthologues. However, the closest BLAST hit is often not the nearest evolutionary neighbour[6], and this problem is exacerbated when using an imcomplete genome, as Pal *et al.* did. We therefore first estimated maximum-likelihood evolutionary distances[7] for multiple, highly significant BLAST hits in the complete genomes, and then used these distances to identify putative orthologues (algorithm by courtesy of D. P. Wall).