erosion of Taiwan at three different timescales. They find both commonality and marked differences in their results. On the oldest rock, where topography is steep, the high erosion rates averaged over the past few million years differ little from those inferred from modern (the past 30 years or less) rates, obtained from ratios of rates of sediment transport by rivers to the areas of their watersheds. On the flanks of the mountainous terrain, where folding and faulting at depth build new topography in weaker rock, present-day erosion rates are highest, despite the low stream gradients and gentle hillslopes, characteristic of slow erosion elsewhere. Moreover, for some of these areas, the average erosion rate obtained from 30 years or so of data exceeds the rates of river incision of narrow valleys over the past 10,000 years. Thus, the modern average erosion rates in these regions cannot have applied to a geological period as short as 10,000 years.

Dadson *et al.* searched for spatial correlations of erosion with factors such as precipitation rate, river discharge, stream gradient and stream power (see below). They conclude that only two correlate well: recent seismicity (Fig. 1), and precipitation associated with typhoons. Earthquakes and large storms are notorious triggers of landslides, which abruptly carry debris to rivers; so these correlations are less surprising than the failure of the other factors. Moreover, the historical record of seismicity on Taiwan goes back only about 100 years, and thus is surely too short to yield a representative image of the distribution of landslide triggers. Perhaps it is no wonder that modern average erosion rates and those averaged over geological times differ in the low parts of Taiwan.

To find a unifying concept for erosion rates, many have turned to stream power. In a precocious effort to understand how running water erodes very weak rock, Howard and Kerby[7] suggested that erosion rates should vary with the stress a flowing stream exerts on its bed, which can be expressed in terms of the discharge and the river gradient, or stream power per unit width. Accordingly, much present work addresses the role of stream power in erosion[8]. Surely the greater the discharge, the faster material can be removed, and abundant evidence shows a correlation of present-day average erosion rates with the steepness of terrain[9,10].

As far as the new work is concerned, Reiners *et al.*[1] and Dadson *et al.*[3] find no correlation between their measured erosion rates and stream power. Burbank *et al.*[2] show that the large variation in rainfall across the Himalaya is compensated to some extent by steeper gradients where rainfall is low, but not sufficiently for them to embrace stream power as the key to account for the poor correlation of erosion rate with rainfall. At the other extreme, Wobus *et al.*[4] exploit the large contrast in stream power between the Greater and Lesser Himalaya as support for the more rapid erosion in one than the other.

Water is Earth's universal solvent, and without it erosion would slow. Yet, as a solution to what makes erosion fast or slow, water's role remains controversial. The differences among these papers call attention to the inadequacy of current theory, without which one gropes for a way to plot data. ■

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Signal transduction

Molecular monogamy

Drew Endy and Michael B. Yaffe

The interactions between cellular proteins must be highly specific, or cells will stop functioning. Some clever protein-manipulation experiments have revealed how this specificity has evolved in yeast.

If an integrated system is to function correctly, its components must be wired together accurately. This requirement presents a particular challenge for living cells, because cellular components move about and intermix, and because the 'wires' themselves are dynamic molecular interactions. In many cells, for instance, protein-based signal-transduction systems are assembled through protein–protein interactions. These interactions are often specified by structurally defined 'domains' in one protein that bind to complementary short, linear amino-acid sequence motifs in another. But even a relatively simple cell such as baker's yeast normally produces more than 4,500 different proteins[1], and frequently several of these proteins contain similar domains or motifs. How, then, do cells wire proteins together with high specificity? On page 676 of this issue, Zarrinpar and colleagues[2] describe one way in which yeast ensures a monogamous protein partnership — by eliminating nonspecific interactions through evolution.

For some types of interaction domains, such as the so-called SH2 and FHA domains, two mechanisms contribute to binding specificity. First, binding occurs only when a particular tyrosine, serine or threonine amino acid in the partner motif has been enzymatically tagged with a phosphate group. The phosphate contributes a large fraction of the total energy required for motif–domain binding[3]. Second, additional amino acids flanking the phosphorylated residue fine-tune the interaction, discriminating between specific and nonspecific partners. But what about other modular domains that recognize more promiscuous motifs, with considerably lower affinity? For instance, how is specificity obtained for SH3 domains, which recognize the core sequence motif proline–X–X–proline (where X is any amino acid)?

This is where the findings of Zarrinpar *et al.*[2] come in. These authors chose to study the interaction between two proteins, Sho1 and Pbs2, from the high-osmolarity glycerol (HOG) signalling pathway in baker's yeast (*Saccharomyces cerevisiae*)[4]. Sho1 is a sensor protein that sits in the membrane of yeast cells and detects changes in external osmolarity. Pbs2 is a signalling protein that coordinates the cellular response to Sho1 activation; the resulting changes in glycerol production help to balance the intracellular and external osmotic pressures. Sho1 and Pbs2 connect through a domain–motif interaction: Sho1 contains an SH3 domain and Pbs2 contains an SH3-binding motif. The SH3 domain in Sho1 is one member of a broader family — there are 27 known SH3 domains in *S. cerevisiae* proteins[2]. But HOG-pathway signalling depends on the specific interaction between Sho1 and Pbs2; cross-reaction with any component from the other 26 SH3-domain–motif pairs could gum up the inner workings of the cell.

Zarrinpar *et al.*[2] start by showing that this doesn't happen (Fig. 1a). They constructed 38 artificial Sho1 proteins by replacing the native Sho1 SH3 domain with one of the 26 other yeast SH3 domains, or with one of 12 such domains taken from multicellular organisms. None of the Sho1 proteins created from the 26 alternative yeast SH3 domains could reconstitute HOG-pathway function *in vivo*. Curiously, however, six of

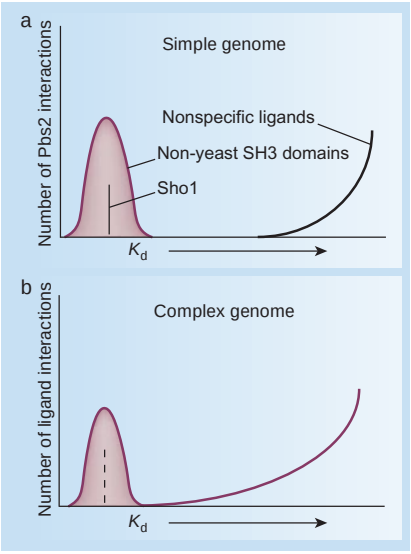

Figure 1 **How organisms achieve specificity of protein–protein interactions. A general feature is the presence of structural 'domains' in one protein and complementary 'motifs' in their binding partners (ligands).** a, **In baker's yeast, which has a relatively simple genome encoding relatively few proteins, a single motif-containing protein (here, Pbs2) binds to just one SH3-domain-containing partner (Sho1) with a reasonably low dissociation constant (K_d; that is, with high affinity). Other yeast SH3-domain proteins bind to Pbs2 with lower affinity (black curve). Zarrinpar *et al.*[2] find that this specificity results from evolutionary negative selection against nonspecific interactions. SH3 domains from other organisms are not subject to negative selection in yeast, and so bind promiscuously to Pbs2 with dissociation constants similar to that of Sho1 (purple curve).** b, **In organisms with more complex genomes, which encode many SH3 domains and many ligands that bind these domains, additional mechanisms may work to restrict a large number of potential interactions (purple curve) to a single domain–ligand pair (dashed line).**

the 12 non-yeast SH3 domains functioned well enough to allow cell growth under high salt conditions (where the HOG pathway is important). Why should this be? Zarrinpar *et al.* suggest that, through natural selection, the amino acids within and around the proline–X–X–proline motif on Pbs2 have evolved to be recognized only by the SH3 domain of Sho1, and not by any other yeast SH3 domain. No such negative selection would have occurred against the non-yeast SH3 domains. In general terms, then, an evolving system composed of intermixing parts could use negative selection to eliminate spurious interactions.

To test this model, the authors changed the Pbs2 SH3-binding motif so as to increase or decrease the strength of the Sho1–Pbs2 interaction. All changes reduced the specificity of interaction for the Sho1 SH3 domain, suggesting that the Pbs2 motif was already 'optimized' for the combination of binding strength and SH3 specificity. As a second test, Zarrinpar *et al.* used a competitive growth assay to compare yeast containing wild-type Pbs2 with yeast containing either a mutant Pbs2 that does not interact with Sho1, or a promiscuous Pbs2 mutant that interacts with both Sho1 and most other yeast SH3 domains. Both the wild-type and the promiscuous strains outgrew the 'non-interacting' strain under high salt conditions. But the wild-type and non-interacting strains outgrew the promiscuous strain under conditions that do not require the HOG pathway. The success of the non-interacting strain under these conditions supports the general model that a cell is better off with components that don't interact than with those that bind to one another indiscriminately. Promiscuous proteins in a particular cell type are selected against in order to maintain a 'self-consistent' protein-interaction network that is free of detrimental interactions.

What happens in more complex animals, in which there are greater numbers of protein–protein interactions (Fig. 1b)? Is negative selection alone sufficiently powerful to maintain interaction specificity? The data here are incomplete. Analysis of some mammalian SH3 domains by techniques such as phage display and bioinformatics suggests more promiscuous protein binding, and a lack of strong, specific motif selection[5]. But some of this apparent promiscuity is clearly overcome by temporal and spatial segregation; not all components are present at the same time and place. So negative selection such as that described by Zarrinpar *et al.* need only operate within the confines of a particular subcellular compartment or cell type in higher animals.

In addition, these organisms may have developed further mechanisms for maintaining interaction specificity. Genomic analyses of multicellular organisms suggest the evolution of more complex multidomain protein architectures[6,7], in which SH3 domains are mixed-and-matched with other modular domains. This might allow a series of weak and otherwise promiscuous individual interactions with any potential target protein to occur simultaneously, with the sum of these interactions providing much higher specificity than that possible with any single domain acting alone.

Zarrinpar and colleagues' work[2] reveals an elegant example of how biology has solved the problem of wiring dynamic systems at the molecular scale. A complete understanding of such systems, and of the mechanisms that underlie their proper function and maintenance, will greatly aid our analysis of — and interaction with — the living world. ■

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Chirality

Organic films with a twist

Michael D. Ward

Left- and right-handed helical molecules form mirror-image chiral crystals on a copper substrate. It seems that the substrate and the molecules work in concert to determine the handedness of the crystal domains.

Chirality is central to the building blocks of life, and to commercial chemical enterprises. Most amino acids, sugars and pharmaceuticals contain chiral carbon centres — a carbon atom bonded to four different substituents in a tetrahedral geometry. Such chiral molecules exist in two mirror-image forms, like left and right human hands, that are called enantiomers. Our understanding of this peculiar property can be traced back to Louis Pasteur, who discovered that 'racemic acid' (a crystalline deposit formed on wine casks during fermentation) consisted of equal amounts of left- and right-handed crystals of sodium ammonium tartrate, which were easily distinguished as mirror images under an optical microscope[1]. As they report in *Angewandte Chemie International Edition*, Fasel *et al.*[2] have exploited the atomic-level imaging capabilities of the scanning tunnelling microscope (STM) to observe chirality directly at the molecular level, in enantiomorphic two-dimensional crystals of chiral molecules on a copper surface.

In three dimensions, chiral molecules can form either racemic (heterochiral) crystals, which contain equal numbers of left- and