

ty, in that allosteric interactions between opposing connexons could generate novel properties. The polarity of voltage gating of Cx46-containing connexons is reversed upon incorporation into an intercellular channel. These results contradict the theory of independent voltage gates and provide a basis for a new model of voltage gating in gap junctions where the voltage sensor of an intercellular channel is not intrinsic to a single connexon, but is shared between, and modulated by, the composition of opposing connexons.

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Extraordinary salmon growth

SIR — Over the past decade, transgenic technologies have been explored in various fish species¹, with particular emphasis on growth enhancement as a strategy to shorten long production cycles. The original gene construct used to double the size of mice used a mouse metallothionein promoter controlling a rat growth hormone gene². This and other mammalian constructs have had no or modest effects on growth in transgenic fish^{3–5}, prompting the development of fish gene constructs^{6,7} with improved effects on growth performance⁷. In addition, public concern over the use of DNA from non-homologous sources makes it desirable to develop constructs from as close to homologous DNA as is practical.

For the production of transgenic Pacific

salmon, we have circumvented some of these problems by developing a gene construct (pOnMTGH1) where all genetic elements were derived from sockeye salmon. This 'all-salmon' construct consists of the metallothionein-B promoter⁸ fused to the full-length type-1 growth hormone gene⁹, and is identical in concept to the construct first used to stimulate growth in transgenic mice².

We microinjected linear pOnMTGH1 DNA into the blastodisc region (animal pole) of coho salmon eggs that were developmentally arrested immediately after fertilization. From more than 3,000 eggs injected, we found that 6.2% of the individuals surviving to one year of age retained pOnMTGH1 DNA in their fin tissue. Control uninjected salmon displayed a uniform frequency distribution of weight classes (Fig. 1a). The group microinjected with pOnMTGH1 had the same modal weight as controls, but, in addition, contained many larger individuals that clearly lay outside the normal distribution (Fig. 1b). Most large individuals were transgenic in fin tissue, indicating that the presence of the pOnMTGH1 construct was responsible for the growth enhancement. Of the large fish that did not have pOnMTGH1 DNA in their fin tissue, 54 per cent were found to be positive in blood cells, confirming the mosaic nature of first-generation transgenic fish. On average, the trans-

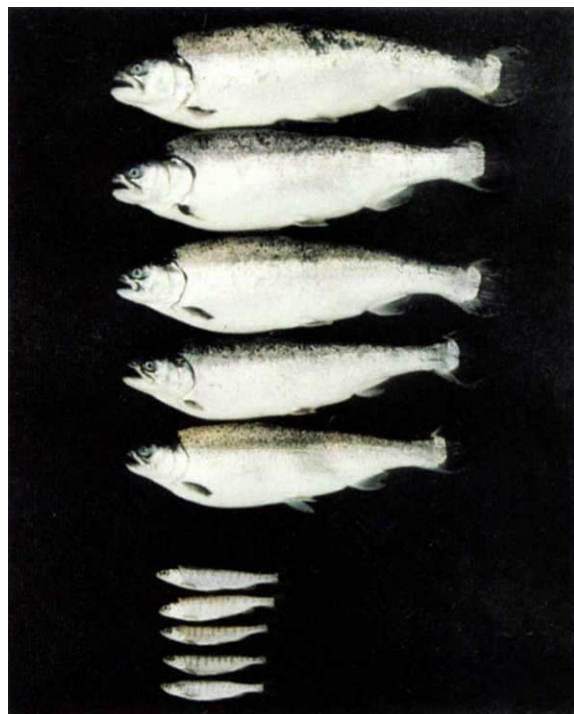


FIG. 2 Non-transgenic (bottom) and transgenic (top) coho salmon siblings at 14 months of age showing size difference and silver appearance of transgenic individuals indicative of transformation to seawater adaptability. Length of top large fish (fork length), 41.8 cm.

genic salmon were more than 11-fold heavier than non-transgenic controls, with a range from no growth stimulation to one individual 37 times larger than controls.

In addition to growth acceleration, most transgenic fish precociously developed a silver body coloration (Fig. 2) typical of salmon undergoing the physiological pre-adaptation (smoltification) necessary for the spring migration from fresh water to the marine environment. Levels of serum growth hormone in juvenile coho salmon are normally very low, then rise in the spring in correlation with smoltification¹⁰. In our experiments, winter levels of growth hormone in transgenic fish were more than 40-fold higher than in non-transgenic controls, indicating that 'unregulated' overexpression of growth hormone from pOnMTGH1 and its consequent physiological effects had

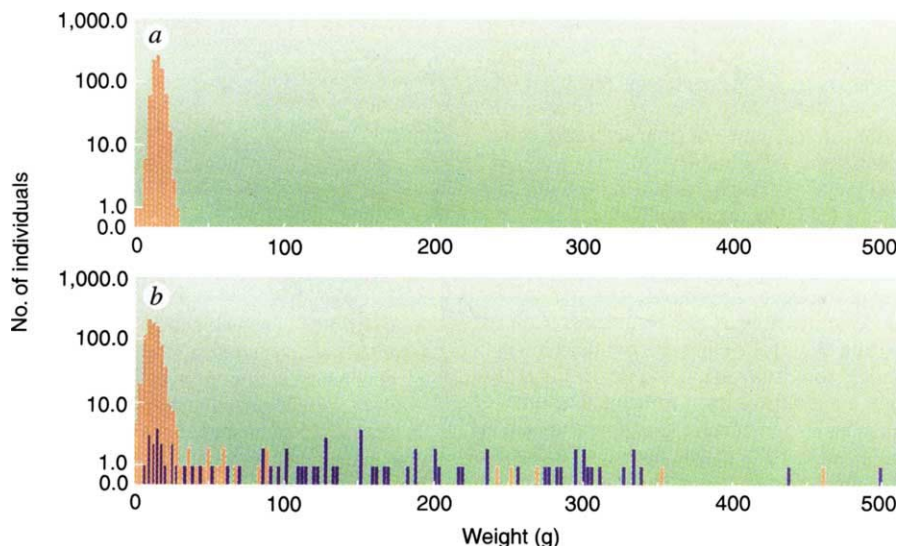


FIG. 1 Frequency distributions of coho salmon weights at 12 months post-fertilization: a, control ($n = 792$); b, microinjected with pOnMTGH1 ($n = 1,073$). Transgenic individuals identified by PCR are indicated by purple bars in b.

1. Fletcher, G. & Davies, P. L. *Genet. Engng* **13**, 331–369 (1991).
2. Palmiter, R. D. *et al.* *Nature* **294**, 611–615 (1982).
3. Guyomard, R., Chourrou, D., Leroux, C., Houdebine, L.-M. & Pourrain, F. *Biochimie* **71**, 857–863 (1989).
4. Zhu, Z. in *Transgenic Fish* (eds Hew, C. & Fletcher, G.) 92–119 (World Scientific, Singapore, 1992).
5. Lu, J.-K., Chen, T. T., Chrisman, C. L., Andrisini, O. M. & Dixon, J. E. *Molec. mar. Biol. Biotech.* **1**, 366–375 (1992).
6. Cavari, B., Hong, Y., Funkenstein, B., Moav, B. & Scharf, M. *Fish Physiol. Biochem.* **11**, 345–352 (1993).
7. Du, S. J. *et al.* *Bio/Technology* **10**, 176–180 (1992).
8. Chan, W. K. & Devlin, R. H. *Molec. mar. Biol. Biotech.* **2**, 308–318 (1994).
9. Devlin, R. H. *Can. J. Fish. aquat. Sci.* **50**, 1738–1748 (1993).
10. Sweeting, R. M., Wagner, G. F. & McKeown, B. A. *Aquaculture* **45**, 185–197 (1985).

been seasonally uncoupled from normal pituitary-derived production.

Although we are encouraged by the growth results observed with Pacific salmon, it remains to be seen whether pOnMTGH1 and other piscine gene constructs will generally function better than non-homologous ones in other cold- and warm-water fish species where growth hormone is limiting with regard to growth performance.

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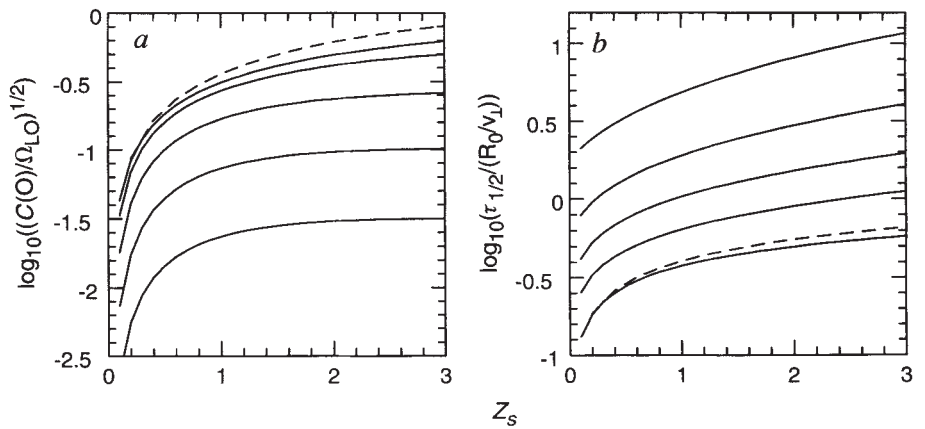
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Quasar variability

SIR—Hawkins¹ monitored the observed variability of quasars with redshifts between 1 and 3, and finds that the timescale of variability decreases with redshift, which he argues is evidence in favour of the quasar light being microlensed by sub-stellar objects along the line of sight. I show here that in fact the timescale of lensing should increase with redshift, because the average redshift of the lensing objects increases with the redshift of the quasar, resulting in a longer variability timescale as the time taken for the object to cross the line of sight is increased by time dilation.

I have calculated the autocorrelation function of the quasar magnitude variations produced by gravitational lensing by a population of intervening, randomly distributed, compact objects, under the assumption that the amplifications A due to lensing by different objects combine multiplicatively. This is exact in the limit of very small lensing probability, and has been shown to be a good approximation up to modest lensing optical depths². It is expected to be a reasonable approximation in the present case. The magnitude change is $\mu \equiv -2.5 \log_{10} A$, so that the contributions of different objects to μ add. For the case that the quasar is a point source at redshift z_S , lensing by a point mass M_L at redshift z_L and distance l from the line of sight amplifies the brightness by a factor $A(u) = (u^2 + 2)/u\sqrt{u^2 + 4}$, where $u = l/R_E$, and $R_E(M_L, z_L, z_S)$ is the Einstein ring radius³. The amplification varies with time due to motions of the observer, source and lens; here I consider only the latter, with lenses moving with a



a, Root-mean-square magnitude variation, $C^{1/2}(0)$; b, variability timescale, $\tau_{1/2}$, as functions of z_s , for different source radii R_S . Solid curves are for $\Omega_0=1$ and $R_S/R_0=0, 0.3, 1, 3, 10$ (decreasing vertically for $C(0)$ and increasing vertically for $\tau_{1/2}$). Dashed curves are for $\Omega_0=0.1$ and $R_S/R_0=0$.

transverse velocity v_{\perp} . The autocorrelation function at time lag τ for a single lens is $\int_{-\infty}^{\infty} \mu(t+\tau)\mu(t) dt$. This is then integrated over l and z_L , assuming a constant comoving number density of lenses, to give the net autocorrelation function $C(\tau) \equiv \langle (\mu(t+\tau) - \langle \mu \rangle)(\mu(t) - \langle \mu \rangle) \rangle$. The characteristic timescale of magnitude variations due to lenses at redshift z_L is just $(1+z_L)R_E/v_{\perp}$, where the factor $(1+z_L)$ results from time dilation.

The autocorrelation function $C(\tau)$, which is symmetrically peaked around $\tau=0$, can be simply characterized by an amplitude and a timescale. The amplitude $C(0) = \langle (\mu - \langle \mu \rangle)^2 \rangle = 0.806 p_L$ gives the mean square magnitude variation. Here, $p_L(z_S, \Omega_{L0})$ is the probability for a strong lensing event ($l < R_E$), also called the optical depth for lensing³, and is proportional to the fraction of the critical density in lensing objects, $\Omega_{L0} = 8\pi G n_{L0} M_L / (3H_0^2)$, but independent of the lens mass M_L . (n_{L0} is the present number density of lenses, and H_0 is the present Hubble constant, taken to be $50 \text{ km s}^{-1} \text{ Mpc}^{-1}$). The timescale, for example the half-width at half maximum $\tau_{1/2}$, is independent of Ω_{L0} , but scales as $\tau_{1/2} \propto R_0/v_{\perp}$ for given z_S . Here, $R_0 \equiv (4GM_L/cH_0)^{1/2}$ is the characteristic value of R_E , and the characteristic timescale $R_0/v_{\perp} = 2.6 \text{ yr} (M_L/10^{-3} M_{\odot})^{1/2} / (v_{\perp}/400 \text{ km s}^{-1})$. The figure shows the dependence of $C^{1/2}(0)$ and $\tau_{1/2}$ on z_S , for total density parameters $\Omega_0=0.1$ and $\Omega_0=1$.

I have also computed the effect of a finite source size, approximating the quasar as a uniform surface brightness disk of radius R_S , following P. Schneider (personal communication). The radii of the optical continuum emitting regions of quasars are uncertain, but are thought to be at least 10^{15} cm for the more luminous quasars. The results are shown in the figure for different values of $R_S/R_0 = 0.3(R_S/10^{15} \text{ cm}) / (M_L/10^{-3} M_{\odot})^{1/2}$. The effect of a finite source size is to decrease the amplitude of magnitude variations and increase their timescale. For $R_S/R_0 \gg 1$, these scale

as $C^{1/2}(0) \propto R_S^{-1}$ and $\tau_{1/2} \propto R_S$; only a fraction of the quasar light is significantly amplified, and the timescale is essentially that for a lensing object to cross the quasar disk.

Hawkins estimates a quantity similar to $\tau_{1/2}$ from his observational data, and finds $\tau_{1/2} \sim 1-5 \text{ yr}$, with the timescale decreasing by a factor 0.6–0.7 with $z_S \approx 1.5$ to 2.5. This is in conflict with the gravitational lensing calculations, which predict that $\tau_{1/2}$ should increase by a factor ranging from 1.2 for $R_S/R_0 \ll 1$ to 1.4–1.6 for $R_S/R_0 \gg 1$, for Ω_0 in the range 0.1–1. The simplest intrinsic variability model predicts that $\tau_{1/2}$ should increase as $(1+z_S)$, that is, a factor 1.4, due to time dilation at the source. In this sense, the lensing model (for point sources) is closer to the observed trend. Another test of the lensing hypothesis would be to compare predicted and observed autocorrelation amplitudes $C(0)$. It would also be useful to carry out numerical simulations of lensing, including the various observational selection effects, to check the accuracy of the assumptions I have made here.

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- Hawkins, M. R. S. *Nature* **366**, 242–245 (1993).
- Pei, Y. C. *Astrophys. J.* **403**, 7–19 (1993).
- Paczynski, B. *Astrophys. J.* **304**, L1–L5 (1986).

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