mode, which is observed when the hyperpolarization of the cell yields a membrane potential below –65 mV, is characterized by a higher signal-to-noise ratio and therefore better signal detectability than the linear summation of tonic firing. For the reconstruction of the input signal switching from burst to tonic firing is then required.

The dualism of feedforward hierarchies on the one hand and intrinsic parallel processing and top-down feedback modulation on the other seems to apply not only to visual cortex and LGN, but also to the primate retina. Whereas Barry B. Lee (Göttingen, Germany) stressed that luminance and chromatic channels are separated already at the level of retinal ganglion or even bipolar cells, Heinz Wässle (Frankfurt, Germany) described the highly interconnected architecture of the inner plexiform layer that lends itself to early parallel processing immediately after the receptor level.

Separate hierarchies and consciousness

The separation of channels for luminance and chromatic signals into the magnocellular and parvocellular pathways, respectively, continues at the extrastriate cortical level with the distinction of dorsal and ventral processing streams. Yet, although at lower levels both pathways are represented in adjacent regions or even interleaved, and cross-talk is therefore anatomically conceivable, the mechanism of interaction between the dorsal and ventral streams in extrastriate visual cortex has for a long time been a source of perplexity. Semir Zeki (London, UK) presented evidence from psychophysical and lesion studies for two separate, largely autonomous systems for colour and motion that complete their perceptual tasks at different times and can be destroyed selectively. Consciousness, or rather awareness, would then have to be modular, possibly enabled by brainstem mechanisms, which Zeki claimed to have identified by functional magnetic resonance imaging of the blindsight subject GY (Ref. 10). The blindsight paradigm might also elucidate the role of the PVC in conscious awareness[11]. However, Michael J. Morgan (London, UK) discussed mechanisms of dichoptic masking and suggested that the dissociation of performance and awareness that has been reported for dichoptic displays and termed 'blindsight in normal observers'[12] might be difficult to replicate[13]. Further topics included the control of eye and eyelid movements (José M. Delgado García, Sevilla, Spain), the development of visual cortical cell properties (Pierre Buisseret, Paris, France; Tobias Bonhoeffer and Frank Sengpiel, Munich, Germany), connectivity patterns of interneurons (Javier De Felipe, Madrid, Spain), colour processing (Stewart H. Hendry, Baltimore, MD, USA), and object recognition (David Van Essen, St Louis, MO, USA; Tomaso Poggio, Cambridge, MA, USA).

The workshop was concluded by a lively discussion about future research strategies, during which Zeki urged the assembled neuroscientists to go beyond the analysis of receptive fields and the transmission of afferent input in order to obtain a new level of understanding of the mechanisms of visual perception. Whereas few of the attendants would be likely to agree that the careful analysis of retinal, thalamic and cortical cell properties has had its time, there was a general consensus that the experimental results presented by Sillito, Orban and others had revealed deficits in the classical receptive-field theory and that some time-honoured dogmas had to be discarded. Or as Gregory would have it: all theoretical mechanisms are imaginary, but some imaginary mechanisms are mythical.

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VIEWPOINT

Mathematical guidance for axons

Geoffrey J. Goodhill

Axon guidance by gradients plays an important role in wiring up the developing nervous system. Growth cones seem to sense a concentration difference across their spatial extent, and convert this into a signal to move up or down a gradient. In this article, a simple mathematical framework is developed to understand when and where gradient detection can occur as a function of gradient shape. This framework is applied to two examples: the guidance of axons by target-derived diffusible factors *in vivo* and in collagen gels, and guidance by substrate-bound gradients of optimal shape, as might be relevant in the retinotectal system. Two distinct spatial limits on guidance emerge: 1 mm for a target-derived diffusible gradient, and 1 cm for a substrate-bound gradient.

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HOW ARE AXONS GUIDED to appropriate targets during development? Although first addressed by Ramón y Cajal over 100 years ago, a new wave of interest in this question has recently been generated by the identification of some of the genes and proteins involved in axon guidance, and the spectacular discovery that many of the mechanisms and molecules are conserved between animals ranging from

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nematodes to *Drosophila* to mammals[1]. One important mechanism is the guidance of growth cones by gradients of attractive or repellent factors[2]. Two ways in which these gradients can be set up are by diffusion (for example, in the guidance of commissural axons to the floor plate in the spinal cord[3]) and by graded expression of guidance molecules in the substrate (for example, in the retinotectal projection[4,5]). What are the theoretical ideas underpinning axon guidance by gradients? Intuitively, they are easy to understand. For diffusible factors, the target releases molecules, which then diffuse creating a higher concentration near the target than further away. For non-diffusible factors local concentrations of transcription factors, can be translated into local concentrations of ligand molecules in the substrate. In both cases, the growth cone evaluates the change in concentration of factor over its spatial extent, and moves in the direction of increasing concentration (or decreasing concentration in the case of repellent factors). However, it is important to analyse these intuitive ideas more quantitatively. A mathematical understanding of what is, and is not, possible by such processes provides quantitative insight into the constraints under which the developing nervous system operates, predicts parameter values, and inspires novel experiments to probe the basic mechanisms of guidance. In this article, some examples are discussed of how simple mathematical reasoning can be used to predict the maximum distance over which guidance could be possible both for a diffusible factor and for a factor expressed in, or bound to, the substrate.

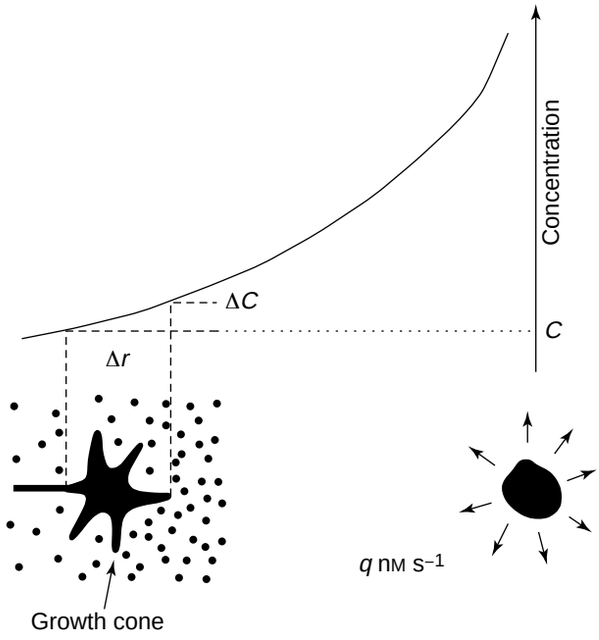

Fig. 1. ***A growth cone encountering a gradient of increasing concentration of a chemoattractant.*** *The spatial extent of the growth cone is Δr, and the concentrations at its two ends are C and C + ΔC. For diffusible factors this gradient can be created by the release of factor (shown as small black circles) from a target (depicted by the uneven shape with arrows, bottom right), shown here at a rate of q nM s^{-1}. Gradients can also be set up in other ways, for example, by translation of morphogenetic gradients. The same ideas apply for chemorepellent factors; in this case, ΔC is converted into a growth signal in the opposite direction.*

Constraints on guidance

Imagine a growth cone that has receptors for a chemotropic factor encountering a gradient of that factor. At one end of the growth cone the concentration of factor is C, while at the other end it is $C + \Delta C$ (Fig. 1). It is plausible to assume that the growth cone senses this difference in concentration ΔC and hence the direction of the gradient by measuring, over some finite time period, the average of the number of receptors bound at one end of the growth cone compared with the other. Although this problem has been analysed mathematically in other biological contexts[6,7], little is known about the particular mechanisms that growth cones use to achieve this feat.

There are three main physical limits that must be considered: first, if the concentration of the factor is too high compared with the dissociation constant for the receptor–ligand complex, almost all the receptors will be bound most of the time, yielding little difference in binding across the extent of the growth cone; second, if the concentration of the factor is too low compared with the dissociation constant, almost none of the receptors will be bound at any given moment, again yielding little difference in binding; and third, the difference in concentration across the growth cone must be large enough to overcome 'noise' in the binding process and in the intracellular signalling that turns a binding difference into directional information (for discussion see Ref. 7). For guidance to be possible at some particular position in the gradient, all of these constraints must be simultaneously overcome at that position. Another prerequisite for a quantitative analysis is to decide which aspect of the change in concentration across the growth cone is most important for gradient detection. Perhaps the simplest aspects to consider are the absolute change ΔC and the fractional change $\Delta C/C$. The latter represents a form of adaptation to a stimulus, and has been implicated in bacterial chemotaxis[8]. Although the sensitivity of growth cones is usually described in terms of percentage (i.e. fractional) changes, there are few quantitative data for growth cones that can distinguish between these two possibilities. The consequences of both will therefore be considered.

Diffusible factors

Target-derived diffusible factors have been implicated in the guidance of axons from the trigeminal ganglion to the maxillary process in the mouse[9,10], in the guidance of commissural axons in the spinal cord to the floor plate[3], and of axons and axonal branches from the corticospinal tract to the basilar pons[11]. The creation, by diffusion, of gradients suitable for imparting positional identity during morphogenesis was analysed mathematically by Crick[12]. He assumed that the important constraint in this case is that, within a few hours, the concentration of factor must reach 99% of its final stable value everywhere in the system. For a model that consists of a point source and a point sink in one dimension, this yields a maximum length scale for such a gradient of about 1 mm. However, the creation of gradients suitable for guiding axons by diffusion poses different constraints: whether or not the concentration of guidance factor is close to reaching its final stable value is no longer important. Rather, what matters is that the three constraints described earlier are satisfied: in particular, the change in concentration across the growth cone must be sufficiently

Box 1. Parameter values and diffusible factors

In order to derive quantitative limits on guidance from the mathematical models described in the text, it is necessary to estimate values for the following parameters: the diffusion constant, the minimum concentration change detectable by the growth cone, the rate of production of diffusible factor by the target, the width of the growth cone, and the maximum and minimum concentrations at which gradient detection is possible. Extrapolating from values measured directly for other molecules[a,b], a reasonable estimate for the diffusion constant D for a molecule such as netrin-1 diffusing through collagen is approximately 10^{-7} cm^2 s^{-1} (Ref. c); the rate of diffusion *in vivo* may be affected by binding to the substrate. The minimum concentration change detectable by a growth cone has been estimated to be about 1% (Ref. d), which is in keeping with quantitative analyses for leukocyte chemotaxis[e]. This gives a fractional change of $\Delta C/C = 0.01$. Both theoretical and experimental results from leukocyte chemotaxis suggest that the smallest concentration change can be detected when the local concentration is equal to the dissociation constant K_D (Ref. e). Therefore, the minimum absolute concentration change detectable is $\Delta C = 0.01K_D$. For some of the molecules implicated in axon guidance, K_D is of the order of 1 nM, a value that can also be derived on theoretical grounds[f]. The rate of factor production q is hard to estimate. Gundersen and Barrett[g,h] directed the movement of a growth cone with NGF released from a pipette at a rate of about 3×10^{-11} nM s^{-1} (Ref. i), while Lohof *et al.*[j] studied growth cone turning in response to cAMP released from a pipette at a rate of 10^{-5} nM s^{-1}. It is argued in Ref. c that 10^{-7} nM s^{-1} is a reasonable estimate for q. The upper and lower concentration limits are taken to be $10K_D$ and $K_D/100$ respectively[k], and a growth cone size Δr of 10 μm is assumed. Consider the concentration gradient created by a diffusible factor specified by the eqn:

$$C = \frac{q}{4\pi Dr}$$

for large time periods (this is easier to analyse than the full time-dependent eqn).

For the fractional-change case, we require:

$$\frac{\partial C}{\partial r}\frac{\Delta r}{C} \geq 0.01$$

(the minus sign can be dropped as the direction of the gradient is irrelevant to the calculation). The maximum guidance distance r_{max} is therefore:

$$r_{max} = 100\Delta r$$

For the parameters above, this gives $r_{max} = 1$ mm. For the absolute-change case, we require:

$$\frac{\partial C}{\partial r}\Delta r \geq \frac{K_D}{100}$$

The maximum guidance distance is :

$$r_{max} = 5\sqrt{\frac{q\Delta r}{\pi D K_D}}$$

Remarkably, for the parameter values quoted above, this is also approximately 1 mm. This estimate is less robust to parameter variation than the fractional-change case, because it depends on q, D and K_D as well as Δr.

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large. In order to calculate the size of this change and how it evolves with time it is necessary to assume a particular model for the diffusion of a factor *in vivo* and *in vitro*. Perhaps the simplest assumption (Fig. 1) is that a small target continuously produces factor at a constant rate into a large volume. This is probably a better model of a three-dimensional (3-D) collagen-gel assay than an *in vivo* situation, where the presence of different types of tissue weakens the uniformity assumption. The concentration of the factor as a function of distance r from the target after time t has elapsed from the start of factor production $C(r,t)$, is then given by:

$$C(r,t) = \frac{q}{4\pi Dr}\,erfc\,\frac{r}{\sqrt{4Dt}}$$

(see for example Ref. 13), where *erfc* is the complementary error function, D is the diffusion constant of the factor through the substrate and q is the rate of factor production by the target. Using this equation and estimates for the parameters (Box 1), it is possible to calculate when and where the constraints mentioned earlier are satisfied, that is, when and where guidance of a growth cone is possible. The fractional-change situation has been analysed in Ref. 14 (see also Box 1). For longer time periods (a few days) after the start of factor production, the maximum range is independent of the diffusion constant and is about 1 mm (Fig. 2). This value fits well with what has been observed in 3-D collagen-gel cultures, and with the fact that target and growth cone are not separated by more than a few hundred micrometers *in vivo* in the case of guidance of axons from the trigeminal ganglion to the maxillary process in the mouse[9,10], or of commissural axons in the spinal cord to the floor plate[3]. This limit is due to the requirement that there is a minimum change in concentration across the growth cone; the minimum-concentration constraint is easily satisfied at this time. The similarity with Crick's value is coincidental, because the two limits come from different models that are subject to different constraints. At earlier time points, however, the factor is more unevenly distributed, being more concentrated around the source. This makes the fractional change larger than at later times, increasing the range over

which guidance can occur (Fig. 2). Depending on the parameters, the model predicts that guidance could be possible at distances of several millimeters before the distribution of factor reaches equlibrium. This is particularly the case for a large molecule that diffuses slowly because the change across the growth cone remains larger for longer. It is conceivable that such a mechanism might be utilized *in vivo* to extend the guidance range beyond the 1 mm limit imposed once the gradient has stabilized. The lower limit on guidance, that is, the distance from the target at which C_{max} is exceeded, is extremely small for the parameters in Box 1; of the order of 10 μm. The absolute-change case is mathematically different. By coincidence however, for the parameters discussed in Box 1, the maximum guidance range is again approximately 1 mm (Box 1). It is now also a function of both D and q: the model predicts guidance over a distance proportional to the square root of q. These theoretical predictions could be used to distinguish between the absolute- and fractional-change cases in a 3-D collagen-gel assay. The absolute-change model predicts guidance over a range that increases with the rate at which factor is released; this could be tested by examining the maximum guidance range for target explants of varying sizes (assuming larger explants release more factor) or for different densities of transfected cells expressing the factor[15]. The fractional-change model predicts no extension of guidance range as the rate of release is varied.

Substratum-bound gradients

For substratum-bound gradients, constraints on gradient shape arise from constraints on how morphogenetic gradients can be translated into gradients of ligand expression. Herwig Baier and the author have recently addressed the question of what is the optimal gradient shape, that is, the shape that would guide growth cones over the maximum possible distance[16]. Given similar assumptions about growth-cone sensing to those used above for the diffusible-factor calculations, the answer turns out to be straightforward[16]. In the absolute-change model, the guidance range is maximized when there is the minimum detectable change in concentration ΔC across the growth cone at every point in the gradient. In this case, the optimal shape is linear and the maximum guidance distance is about 1 cm (using the parameters in Box 1). In the fractional change model, the guidance range is maximized when there is the minimum detectable fractional change in concentration $\Delta C/C$ across the growth cone: now, the optimal shape is exponential. However, the maximum guidance distance is again about 1 cm. These two cases are compared in Fig. 3. This distance of 1 cm represents an upper limit on guidance distance, because it assumes that a growth cone can sense, over a very wide concentration range, the smallest change in concentration it is capable of detecting when the concentration is optimal (equal to the dissociation constant).

To guide axons over longer distances, several gradients of different ligands spaced at regular intervals could be imagined. It is possible that such a mechanism might operate in the retinotectal system[16]. The length of the developing tectum is of the order of 1 cm, and axons might be guided to appropriate targets by gradients of attractive and repellent molecules[17,18].

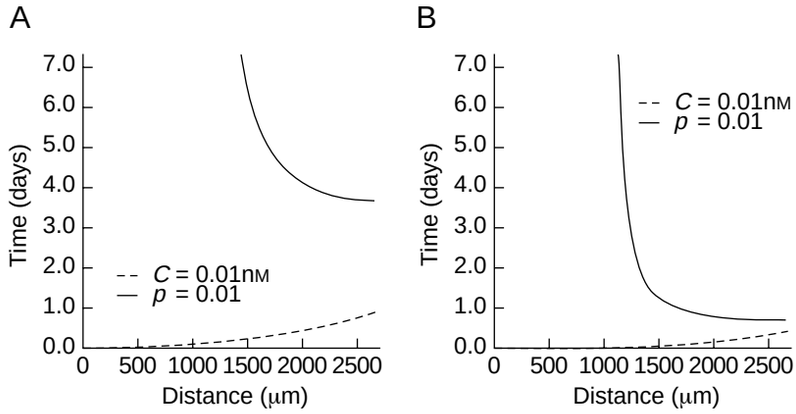

Fig. 2. ***Interaction of constraints for guidance by a diffusible factor with molecules of different sizes.*** **(A)** *Interaction of constraints for guidance by a diffusible factor in the fractional-change model for a large molecule with a diffusion constant* D = 10^{-7} cm^2 s^{-1}. **(B)** *Interaction of constraints for guidance by a diffusible factor in the fractional-change model for a slightly smaller molecule with* D = 5 x 10^{-7} cm^2 s^{-1}. *(*D *is expected to scale approximately inversely with the cube root of the molecular weight). Both graphs show the time at which two constraints are satisfied at each distance: the low concentration limit, labelled* C*, where not enough receptors are bound for a gradient signal to be detected (assumed to be* $K_D/100$ *with* K_D = 1 nM*), and the fractional-change constraint, labelled* p *(assumed to be* $\Delta C/C$ = 1%*). The region between the two curves in each graph represents where guidance is possible. In both cases, the guidance limit imposed by the fractional-change constraint, once the gradient has stabilized, is 1 mm. However, guidance range is extended at earlier time points, when the fractional-change constraint has yet to take full effect. This is particularly apparent for the slowly diffusing molecule (*D = 10^{-7} cm^2 s^{-1}*) shown in* (A).

Two recently identified molecules that are expressed in gradients in the tectum are ephrin-A5 (formerly RAGS)[4] and ephrin-A2 (formerly ELF-1)[5,19]. Both bind to members of the Eph family of receptors, some of which are expressed in gradients in the retina (reviewed in Ref. 20). The ephrin-A2 gradient spans the entire tectum, whereas the ephrin-A5 gradient is shifted posteriorly in the tectum and is absent from the anterior tectum (where retinal axons enter)[4,5,19]. Ephrin-A5 has a significantly higher affinity than ephrin-A2 for the Eph receptors EphA3 (formerly Cek4), EphA4 (formerly Cek8) and EphA5 (formerly Cek7), which are expressed in gradients in the retina[21].

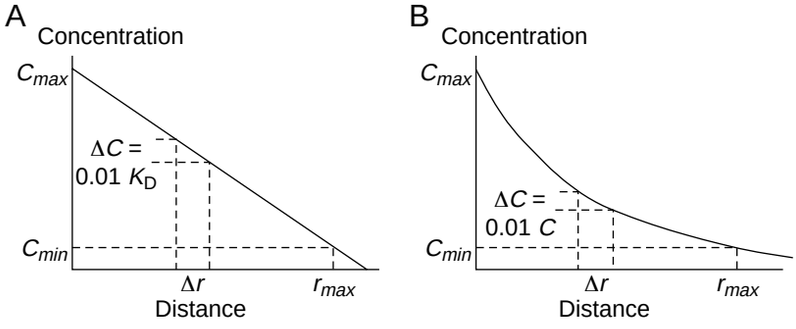

Fig. 3. *The shape of the gradient that gives guidance over the maximum distance is determined by the gradient reading mechanism.* **(A)** *In the absolute-change case, the optimal gradient is linear and the maximum guidance range is given by:*

$$r_{max} = \frac{\Delta r}{p}\frac{C_{max} - C_{min}}{k_d}$$

where p *is the minimum fractional change detectable by the growth cone (assumed to be 1%).* **(B)** *In the fractional-change case, the optimal gradient is exponential and the maximum guidance range is given by:*

$$r_{max} = \frac{\Delta r}{p} log_e \frac{C_{max}}{C_{min}}$$

For the parameter values given in Box 1, r_{max} *is about 1 cm in both cases. See Ref. 16 for further details.*

It is thus possible that ephrin-A5 could take over guidance by acting on the same receptors as ephrin-A2 when the concentration of ephrin-A2 becomes too high to provide an effective guidance signal[16]. Also, the two guidance mechanisms make different predictions about optimal gradient shapes (linear versus exponential), and it might thus be possible to distinguish them by detailed measurement of gradient shapes *in vivo*.

Discussion

For a target-derived diffusible factor, a simple mathematical analysis suggests a maximum range of guidance by the gradient of about 1 mm. The maximum guidance range possible by a single gradient of optimal shape is about 1 cm. What are some of the principal assumptions and simplifications that have been made to derive these limits? First, it was assumed that the growth cone is the only part of the neuron involved in gradient sensing, which allows straightforward analogies with leukocyte chemotaxis. If the axon shaft also expresses receptors for the guidance molecule, it could, in principle, compare the amount of ligand bound at different parts along its length in order to detect the gradient. This could increase Δr, and thus the maximum guidance distance predicted by the model, by several orders of magnitude. There are certainly cases where the axon shaft displays sensitivity to diffusible ligands, for example in the generation of branches from corticospinal axons in response to cues from the basilar pons[11]. However, more generally, axons have not been shown to exhibit the exquisitely sensitive responses to guidance cues that have been demonstrated for growth cones[22,23], and there is currently no direct evidence for an integration of information regarding the amount of ligand bound between widely separated parts of the axon.

Second, it was assumed that the growth cone integrates binding information across its spatial extent to determine the direction of the gradient in a similar manner to leukocytes, rather than adopting a temporal mechanism analogous to that used by bacteria. Bacteria compare local concentrations over time, and randomly reorient their direction of motion ('tumbling') with a frequency that depends on whether the concentration they detect is increasing or decreasing (reviewed in Ref. 24). However, the paths followed by individual bacteria in a gradient are therefore biased random walks, while time-lapse imaging of individual growth cones shows that they follow much smoother paths than this[22,25]. In addition, bacteria and growth cones operate in radically different parameter regimes. Bacteria are small and fast, moving at speeds of the order of 20 cell diameters per second[26]. A growth cone of size 10 μm on the other hand, moving at about 1 mm per day, takes about 15 min to move one growth cone diameter. The time over which a 'memory' for a previous concentration would need to be maintained in a growth cone is therefore about four orders of magnitude longer than that for a bacterium. Such an extended recall of precise levels of receptor binding seems unlikely. Individual filopodia move on a much faster timescale and so could perhaps use a temporal comparison mechanism; however, because the growth cone is effectively stationary during this time, this reduces to a spatial comparison across the width of the growth cone.

Third, the influence of the growth cone on the gradient has been neglected. For example, at a local concentration of K_D, half of the molecules in the vicinity of the growth cone should be bound. Although this introduces a local perturbation of the gradient, unless there is an extremely high density of growth cones, the effect on the shape of the gradient on a larger scale is negligible. The average time for a molecule to diffuse across a distance of the extent of the growth cone (using the parameters in Box 1) is about 1 s, and therefore the missing molecules can quickly be replaced from the surrounding volume.

Fourth, the tissue or collagen gel has been assumed to have infinite volume. With the parameters given in Box 1, the average concentration in a finite block of tissue of side length 1 mm becomes quite large quite quickly. In reality, factors are probably removed by localized or distributed sinks. The effects of two types of distributed sinks are discussed in Ref. 14. If a reversible binding process is assumed, so that the amount of factor bound at any time is proportional to its local free concentration, the effective diffusion constant will be reduced, but the gradient will be otherwise unchanged. If, instead, the factor is irreversibly removed everywhere, at a rate proportional to the concentration, the concentration is simply multiplied by an exponential factor that decays with time. The rate of decay is the proportionality constant between the rate of binding and the free concentration. In both cases the 1 mm limit is unaltered in the fractional-change model.

The approach taken in this paper can be thought of as being at a 'thermodynamic' level of description. The bulk constraints on guidance that have been analysed arise from processes occurring at a lower, 'statistical–mechanical' level. As a physical analogy, the specific heat capacity of solids is treated as a parameter to be measured in classical thermodynamics. A statistical–mechanical level description derives this parameter from an analysis of the thermally induced oscillations of individual molecules within a solid. A statistical–mechanical level model for growth cone guidance would include details such as: the statistics of receptor binding; the timescale over which the growth cone integrates binding information to determine direction; the distribution of receptors over the filopodia, lamellipodia and body of the growth cone; the intracellular signalling systems that link receptor binding to a directed movement signal; and the dynamics of changes to the cytoskeleton. A complete quantitative analysis at this level would allow the bulk-level constraints to be explicitly derived, directly address the question of the relative importance of absolute versus fractional changes, and allow the above estimates of maximum guidance range to be substantially refined. A model at this level, however, requires numerous assumptions to be made about mechanisms and parameter values that are currently underconstrained by experimental data. An advantage of the thermodynamic-level approach is that it is not concerned with the details of these lower-level mechanisms, but operates only with their directly measurable, higher-level consequences.

The evolutionary significance of absolute spatial limits on axon guidance by gradients has not been explored. The anatomy of a system where guidance is required over a few hundred microns in a mouse embryo cannot just be scaled up to give equivalent guidance in a

larger embryo. Unfortunately, it is hard to develop this argument further at present: there is very little data about the timing of axon guidance events in large animals, and thus the spatial separation between axons and target at the time guidance is required is unknown. A quantitative consideration of the factors that constrain axon guidance by gradients leads to both a deeper understanding of the biological system and suggestions for new experiments. As discussed earlier, it might be possible to distinguish between the absolute- and fractional-change models by appropriate measurements *in vivo* and in collagen-gel assays. From an experimental point of view, it would also be useful to apply to growth cones the kind of quantitative investigations using known gradients of controlled form that have been used to characterize chemotaxis in bacteria[8] and leukocytes[27]. Only then will a truly quantitative description of axon guidance by gradients emerge.

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Simulation in neurobiology: theory or experiment?

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Investigation in neurophysiology usually involves measurements of large population-average signals or small sample recordings. There is an underlying assumption that the observations express activity of large groups of similarly acting neurons that is the result of a bottom-up scenario in which individual cells, via their synaptic interactions, lead to the large scale phenomena. The connection between the levels must be provided by theory, which must also provide the relevant variables for observation. It is suggested that between the experiment and the full theory there is a creative, mixed role for simulation: both experimental and theoretical. A simulation presents complex dynamics and hence is an empirical board for testing theoretical tools, yet its controlled behaviour can make predictions about the biological system.

Trends Neurosci. (1998) 21, 231–237

NEUROPHYSIOLOGY AIMS to decipher the behaviourally relevant dynamics of large assemblies of neurons. Experiments involve either the measurement of behaviour of small samples of neurons (as in electrode recordings) or averaged signals of large numbers of neurons (such as with EEG and MRI). Phenomena observed in electrode sampling must represent large scale features or they would not be detectable. Signal averages (from several million cells and over tens of cortical mm^2) are of interest if they represent the concerted dynamics of neurons and synapses; some notion that connects the presumed underlying structure of neurons and synapses to the large scale dynamics is needed, and this requires a theoretical framework. The details of the underlying system are not fully understood, nor is the level of detail required for the production of the sampled or averaged phenomena. One way to proceed is to set up models for the system, simulate them, and compare the behaviour of the simulated system to an accompanying theory whose role it is to identify the relevant global degrees of freedom on the one hand, and to sample recordings from brain on the other hand. Large-scale simulation is becoming an ever more prominent feature in the study of neural systems from detailed, small scale descriptions of single cells such as cable theory models[1–3], to large scale networks of simplified neurons[4–6] that exhibit various types of collective dynamics. In-between these two extremes are simulations that combine complex ionic, neurotransmitter and neural structure with large scale features[7]. However,

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