A Bayesian model predicts the response of axons to molecular gradients

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Axon guidance by molecular gradients plays a crucial role in wiring up the nervous system. However, the mechanisms axons use to detect gradients are largely unknown. We first develop a Bayesian “ideal observer” analysis of gradient detection by axons, based on the hypothesis that a principal constraint on gradient detection is intrinsic receptor binding noise. Second, from this model, we derive an equation predicting how the degree of response of an axon to a gradient should vary with gradient steepness and absolute concentration. Third, we confirm this prediction quantitatively by performing the first systematic experimental analysis of how axonal response varies with both these quantities. These experiments demonstrate a degree of sensitivity much higher than previously reported for any chemotacting system. Together, these results reveal both the quantitative constraints that must be satisfied for effective axonal guidance and the computational principles that may be used by the underlying signal transduction pathways, and allow predictions for the degree of response of axons to gradients in a wide variety of in vivo and in vitro settings.

axon guidance | chemotaxis | growth cone | nerve growth factor | nerve regeneration

Endogenous chemical gradients are a key source of information used by developing axons when wiring up the nervous system. Furthermore, artificially generated gradients are a potential therapy for restoring connectivity after neural injury. Many of the molecular gradients that direct axons in the developing nervous system have recently been identified, together with some of the signaling pathways through which they operate (1–8). However, our understanding of the mechanisms by which axons actually detect gradients remains qualitative. This limits our ability to predict both the response of axons when gradients are perturbed and the optimal parameters for promoting regrowth after injury.

To be guided by a gradient, axons must be able to detect small spatial variations in receptor binding. This requires integrating signals from spatially distributed receptors to make a decision as to the direction of the gradient. Resources within the growth cone can then be marshaled appropriately by this information, for instance, via the production of steep gradients of intracellular signaling molecules (8). Although there is evidence for a role for gradients of molecules such as Ca^{2+} in this latter step (9, 10), very little is known about the computations required to accurately make the initial decision.

What constrains the ability of an axon to make a decision regarding gradient direction? Both experimental and computational work addressing chemotaxis in related systems such as bacteria, leukocytes, and *Dictyostelium* has identified the fundamental role of noise in limiting gradient perception. Noise can arise from low numbers of ligand molecules, from the stochastic nature of receptor binding, and from intracellular signaling pathways (11–16). Such constraints must also apply to axonal gradient sensing (17, 18), but the implications of this for under-

standing axonal responses both in vivo and in vitro have not been systematically explored.

Noise in gradient sensing is a form of uncertainty in sensory information processing. In recent years, a “normative” (usually Bayesian) approach has proved to be a powerful technique for understanding how biological nervous systems deal with sensory uncertainty (19–22). This approach dissects the computational logic of complex behaviors by comparing actual, observed performance with the best performance possible given the information that is available to this system. However, barring a few exceptions (e.g., refs. 23, 24, and 25), such an approach has been applied predominantly at the systems, rather than molecular, level.

In the first part of this article, we develop a Bayesian model for the optimal determination of gradient direction based on combining measurements from noisy, spatially distributed receptors. This model allows us to predict analytically the proportion of correct decisions an axon should make about gradient direction as a function of gradient steepness and absolute concentration. In the second part of this article, we directly test this prediction. In particular, we perform the first large-scale experimental investigation of the dependence of the response of rat early postnatal dorsal root ganglion (DRG) axons on the steepness and concentration of gradients of nerve growth factor (NGF). We examine the strength of response of DRG axons for 4 different NGF gradient steepnesses, each over several orders of magnitude of NGF concentration (38 different combinations of steepness and concentration in total), by using an assay we recently introduced that allows precise control over these parameters (26, 27). This provides by far the largest dataset yet presented for how axonal response to gradients varies with gradient parameters. Remarkably, these data fit well with our Bayesian model, thus directly validating our analytical prediction for chemotactic performance.

Results

Bayesian Model of Spatial Gradient Sensing. A fundamental constraint on the performance of any chemotaxing system is random fluctuations in the pattern of receptors that are bound at any instant (11, 16). This means that, even if there were no thermal noise in the number of ligand molecules available for binding, it is still possible that the instantaneous pattern of binding will not accurately reflect the external gradient conditions. It is therefore important to consider how, given this fundamental uncertainty,

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Fig. 1. Bayesian model of spatial gradient detection. (A) Model growth cone (for more detail see Fig. S1). Receptors on the surface bind ligand molecules probabilistically according to standard Michaelis–Menten kinetics. Signals from the bound receptors are then combined in the growth cone to optimally decide the most consistent gradient direction for that pattern of ligand binding. Although there are several intuitively obvious decision rules the growth cone could employ, determining the provably optimal strategy is nontrivial. We show that the optimal rule is to weight the signal from each bound receptor by its distance from the center of the growth cone (see *SI Text*). The sizes of the growth cones in the bubble represent the degree of belief of the growth cone in the 2 hypotheses for gradient direction based on that particular pattern of receptor binding. (B) Chemotactic sensitivity curves calculated analytically for the optimal decision rule for the gradient parameters used experimentally. The percentages refer to the fractional change in concentration across 10 μm . We set $K_D = 0.3$ nM based on the best fit between the model and the data (see Fig. 3).

a chemotacting system such as an axon could best make a decision about gradient direction.

Inspired by its success in other biological domains, we therefore developed a Bayesian “ideal observer” model (22) to determine the optimal strategy by which any gradient-sensing device can most reliably extract directional information from a set of intrinsically noisy receptors distributed across its spatial extent (Fig. 1A). The model is described in more detail in the supporting information (*SI Text* and Fig. S1). Briefly, we considered a 1-dimensional growth cone* with N randomly distributed receptors, exposed to a ligand gradient such that μ

is the relative change in concentration across its spatial extent, and γ is the concentration at the center of the growth cone relative to K_D . We calculated the likelihood function giving the probability of each pattern of receptor binding in terms of μ and γ . Using Bayes’ theorem, we then inverted this function to give the posterior probability of μ given the pattern of binding, assuming that the prior probability for μ is symmetric and concentrated near zero. The gradient direction is then estimated by comparing the posterior probabilities that the gradient points in one direction versus the other.

There are many obvious possibilities for how to combine information from spatially distributed receptors to determine gradient direction, perhaps the simplest being to add up the total amount of receptor binding on one side of the growth cone and compare it with the total amount of receptor binding on other side. However, the use of the Bayesian approach allowed us to determine the optimal strategy, i.e., the one that gives the most reliable estimate of gradient direction. We found that this optimal strategy is to calculate the sum of the positions of bound receptors, i.e., weighted by their distances from the center of the growth cone. That is, receptor binding at the extremities of the growth cone contributes more weight to the decision than receptor binding near the center. In *Discussion*, we consider several possible biological implementations for this optimal computation.

Predicting Performance as Gradient Parameters Are Varied. Variations in receptor binding statistics over the spatial extent of the growth cone are determined by the gradient steepness and the absolute concentration. We therefore asked how the performance of our Bayes-optimal growth cone should vary with these parameters. Our readout of performance in the model is the probability that the growth cone estimates the direction of the gradient correctly for given gradient conditions. We were able to show analytically (see *SI Text*) that this proportion of correct decisions given steepness μ and concentration γ is

$$P_{\text{correct}}(\gamma, \mu) \approx \frac{1}{2} + \sqrt{\frac{N}{24\pi}} \mu \sqrt{\frac{\gamma}{(1 + \gamma)^3}}$$

Thus, the model predicts that axonal response should be determined by a scaling constant times $\mu\sqrt{\gamma/(1 + \gamma)^3}$. We refer to this quantity as the signal-to-noise ratio (SNR). This SNR is plotted against absolute concentration for the same gradient steepnesses we subsequently used experimentally (Fig. 1B), using the value of the dissociation constant K_D we determined as described below. Our analysis does not depend on how the decision regarding gradient direction influences growth cone behavior, which could be, for instance, a turn or a change in growth rate. In *SI Text*, we also discuss the relative performance of alternative strategies for weighting receptor binding measurements.

Experimental Analysis of the Dependence of Axonal Response on Gradient Conditions. Testing the above theoretical prediction for performance requires assaying the degree of response of axons to a range of different gradient steepnesses and concentrations. As a robust model system, we therefore examined the response of early postnatal rat DRG explants to gradients of NGF (28) after 2 days in collagen gels (see refs. 26, 29, and 30). Gradients were generated by using a more refined version of the technology described in ref. 26 (see *Materials and Methods* and Movie S1). In particular, by printing precisely controlled concentrations of ligand at precisely defined locations on the surface of a collagen gel, we created gradients in the gel for which, at particular positions, both the gradient steepness and absolute concentration remained relatively stable for periods of days (26, 27). We printed exponential gradients of ligand of steepnesses 0.12, 0.18,

*For simplicity we phrase our discussion in terms of making comparisons across the extent of only the growth cone. However, our arguments are not affected by whether the comparison takes place over a longer spatial range, for instance including part of the axon shaft.

Fig. 3. Match between model and data. Measured guidance ratio plotted against the signal-to-noise formula predicted by the model. Error bars are SEMs. The red line is a linear fit (Pearson's $r = 0.90$). For the dependence of the fit on K_D see Fig. S5B

despite the similarity in the difference number of bound receptors with the previous example. This illustrates that the observed response depends nontrivially on concentration and gradient steepness.

Experimental Data Are Predicted by the Bayesian Model. The above calculations make it clear that the axonal response depends in a nontrivial way on the gradient conditions. But is this quantitatively the dependence predicted by the Bayesian model? It is not possible to predict the absolute level of asymmetry observed in our experimental explants, because this depends on many unknown biological details of how axons convert decisions about gradient direction into directed motion. Rather, we can compare the way the response varies with gradient parameters between the model and the experiments. To do this quantitatively we plotted the SNR value predicted by the model against the experimentally measured guidance ratio for each of the 38 conditions in our experiment (Fig. 3). It can be seen that there is a remarkably strong correlation between the 2 sets of values (Pearson's $r = 0.90$). The only free parameter in this fit is the dissociation constant K_D . The K_D that maximized the correlation between the predicted SNR and the guidance ratio was 0.3 nM, which agrees well with the positions of the peaks in the guidance and outgrowth curves of Fig. 2 and Fig. S3A (the dependence of the correlation on K_D is shown in Fig. S5B).

Discussion

Comparison with Data from Conventional Collagen Assays. Our experimental data offer the first complete quantitative analysis of the behavior of axonal growth cones in molecular gradients and reveal sensitivity substantially more extreme than previously reported (26). The response of explants to gradients has been one of the key methods driving the field of axon guidance (5). However, this is usually in the context of the more conventional collagen gel coculture assay (31–34), where the gradient parameters are unknown and uncontrolled. Conventional collagen assays also suffer from variations between dishes in variables such as target size and thus the amount of factor released, separation between the explant and the ligand source, and transfection efficiency, all of which affect the molecular gradient experienced by the growth cones (35, 36). In contrast, in our more controlled assay we have shown that measurably different degrees of outgrowth asymmetry can be observed for remarkably subtle changes in gradient parameters. These variations may help explain some of the variability in the responses seen in conventional collagen assays.

Fitting the Model to the Data. Our ideal-observer model reproduces the overall variation in axonal behavior with gradient parameters by fitting only one parameter, the receptor-ligand dissociation constant K_D . The chemotropic response of growth cones to NGF is mediated by TrkA and p75. Although it was previously thought that both high- and low-affinity binding sites exist for NGF binding to TrkA/p75 (37), recent Scatchard analysis suggests that there is only 1 binding site with $K_D = 0.9 \pm 0.3$ nM (38). This is consistent with our determination of a similar value for K_D by using quite different methods.

It is remarkable that our data can be fit so well with a model that only considers the noise in the instantaneous receptor binding pattern. Noise inherent in thermal fluctuations in ligand numbers and in intracellular signaling pathways would be expected to provide additional constraints on performance, although potentially offset by temporal averaging of receptor binding measurements (11–15, 39). However, although reality is undoubtedly more complex than the situation represented in our model, this does not undermine the usefulness of our closed-form solution as a predictive tool for axonal responses.

Quantitative Implications. These calculations illustrate clearly that the level of response depends not on the absolute difference in receptor binding levels but on a nontrivial combination of gradient steepness and absolute concentration. We have been able to quantitatively capture this relationship from first principles in a simple analytical formula. Once more quantitative data becomes available for the gradients existing in vivo, it will be possible to use this equation to make precise predictions for how the fidelity of guidance should vary along a pathway, and to what degree perturbations in the gradient should affect guidance. Our equation can also be used to make quantitative estimates for how guidance should vary with parameters such as space, time, and rate of chemotropic factor production in in vivo situations and more conventional collagen gel coculture assays (35, 36).

Clearly the differences in average binding calculated above would need to be amplified by downstream processes to produce a response. This might involve, for instance, movement of receptors toward the up-gradient side (40). However, such amplification is only useful once the direction of the gradient has actually been detected and so is not a reliable mechanism for the detection itself. It is possible that the comparison may be occurring over a longer distance than the width of an individual growth cone, for instance, by taking into account information from receptors on the axon shaft. However, although this would change the details of the numbers calculated above, it would not change the optimal strategy we have determined for comparing information from spatially distributed receptors or its quantitative fit to the measured responses (due to the unknown scaling constant). It is also possible that, by internalizing bound NGF, the local gradient conditions are perturbed by each growth cone. However, for this to have an impact on our overall conclusions, it would be necessary for the perturbations to somehow amplify the SNR. Analogously to the remarks above regarding amplification by receptor redistribution, amplification by differential NGF uptake presupposes that the direction of the gradient has already been correctly determined.

Asymmetry with Concentration in the Guidance Response. Our model also offers a simple explanation for the asymmetry in chemotactic sensitivity seen in Fig. 2B. We assume that the growth cone has knowledge of the gradient only through the signals produced by its bound receptors. However, because of stochastic fluctuations in receptor density across the width of the growth cone, it will inevitably be the case for shallow gradients that occasionally, the receptor density fluctuations will be large enough to

dominate the true gradient signal. For the case of low ligand concentrations, few receptors are bound, and the size of this effect is small. However, as the ligand concentration increases the proportion of bound receptors increases, and thus the bias in the downstream signal due to nonuniform receptor density also increases, reducing the accuracy of decision making.

Possible Implementations of the Optimal Chemotaxis Strategy. We have shown that the optimal strategy is to calculate the sum of the positions of bound receptors weighted by their distances from the center of the growth cone. It is useful to think of this weighted sum as the difference in signal strength between the 2 sides of the growth cone. Implementing the optimal strategy then involves 2 steps: correctly weighting the inputs from the receptors so that receptors contribute in proportion to their distance from the center and then deciding whether the resulting signal is stronger on one side or the other. One possibility for how the growth cone might achieve the weighting step is by maintaining an inhomogeneous distribution of receptor-coupled effector proteins, with effector concentration proportional to the distance from the center of the growth cone. Peripheral receptors would then be presented with a greater number of effectors than central receptors, thus contributing more to the signal strength. Although direct evidence for or against this does not exist in growth cones, in *Dictyostelium* the most obvious candidate molecules for this role—various forms of G proteins—are known to be uniformly distributed across the leading edge (41), arguing against this possibility. Alternatively, the growth cone might preferentially distribute its receptors to the extremities, i.e., to the tips of filopodia. Some classes of guidance cue receptor have been observed to redistribute in the presence of a gradient—for example, on stimulation by a GABA gradient, GABA receptors cluster on the up-gradient side of rat spinal neuron growth cones, before a noticeable response occurs (40).

However, the analysis of the dynamical model of gradient detection of Skupsky et al. (42, 43) motivates a third alternative based on the properties of intracellular reaction diffusion pattern formation process triggered by receptor binding events. In the model presented in ref. 43, polarized cells are most sensitive to local environmental perturbations in concentration, which impinge at an angle of $\approx 60^\circ$ to the axis of polarization. This naturally awards peripheral receptors greater influence than those closer to the polarization axis. Although these authors focused on eukaryotic cell chemotaxis, similarities with the signaling networks underlying growth cone chemotaxis suggests that their results may also be relevant for growth cones (8, 44). The decision process itself, i.e., choosing the side on which the weighted signal is greatest, could then be implemented through adaptation and positive feedback, tuned to the appropriate length scale (8).

As discussed in the *SI Text*, some approximations to the Bayesian strategy have a lower absolute level of performance, but still produce a similar variation in performance with gradient parameters (see Fig. S6). Thus, it may be possible to achieve close to optimal performance by strategies that make less implementation demands on the growth cone than the optimal strategy. To directly measure implementation strategies would require a far more detailed analysis than has yet been performed experimentally of the spatiotemporal variations in distributions of signaling molecules inside growth cones exposed to gradients.

Conclusions

Ultimately, the quantitative predictions offered by our model allow a more precise understanding of in vivo events during both normal and abnormal nervous system development, and may facilitate the design of gradients that optimize the ability of the

nervous system to rewire itself after injury. Overall, these results suggest that optimality principles already demonstrated to be effective at the systems level will also be useful for understanding sensory information processing at the cellular level and point to directions for the quantitative understanding of nervous system development.

Materials and Methods

Tissue Preparation. DRGs were removed from the thoracic and lumbar regions of postnatal day P0–P3 rat pups, trimmed and stored in Hibernate E (phenol red; Brainbits) at 4 °C overnight. On the next day, the outer capsule was digested for 12 min in 0.25% trypsin/10 μ g/mL DNase1/Ca²⁺ and Mg²⁺ free Hanks's balanced salt solution. The explants were centrifuged and resuspended in Leibowitz's L-15 medium containing L-glutamine and 0.45% D(+)-glucose 3 times.

Dry Collagen Gels. A 0.2% collagen gel solution was prepared on ice by mixing rat tail type I collagen stock solution (BD Biosciences) diluted with water to contain 0.2 mg/mL collagen, 27 μ L of a 7.5% sodium bicarbonate solution per milliliter of original collagen stock, 1 $\times$ OptiMEM (Gibco) and a mixture of 100 μ g/mL penicillin, 100 μ g/mL streptomycin, and 250 ng/mL amphotericin (Gibco). Collagen gels were prepared and 6 explants plated in a row in 35-mm tissue culture dishes as described previously (26).

Gradient Generation. Gradients of NGF (GroPep) were created by using a Nano-Plotter 2.0 (Gesim). The physical principles of gradient generation were as previously described (26, 27), but the precise details were different because of the greater flexibility of the Nano-Plotter compared with the technology used in ref. 26. Twelve stock solutions with exponentially increasing NGF concentration were “printed” onto the surface of the collagen gels in the form of 12 parallel lines 20 mm long and 1 mm apart, each line containing the same volume of stock (see Movie S1). Line 4 coincided with the position of the row of explants. The amount of NGF required in each line to produce the desired final concentration in the gel was calculated as previously described (26, 27). However, we also calculated correction factors for both the concentration and gradient steepness, to take into account the average gradient conditions existing over the complete time course of the experiment (see *SI Text* and Fig. S2). Four additional “pregradient” lines of only vehicle (0.1% BSA/PBS) were applied adjacent to the low-concentration side of the gradient (line 1) to avoid a possibly confounding gradient of collagen density near to the explants. After printing, dishes were returned to a 37 °C incubator with 5% CO₂ for a total explant incubation time of 40–48 h. Our standard control was to print a “plateau” by using the same methods, except with no change in NGF concentration between the different stocks. For delayed application of gradients (Table S3), DRG explants were embedded in collagen gel containing 0.1 nM NGF and a gradient resulting in 0.24% steepness with 0.3 nM NGF at the explant printed either immediately or after 2, 4, 8, 12, 18, or 24-h incubation at 37 °C.

Neurite Visualization. Explants embedded in collagen were fixed with an equal volume of 10% formaldehyde/0.1% Triton X-100 in PBS overnight. After 5 washes with PBS for 1 h each, explants were incubated overnight in 1 μ g/mL of the neuronal tubulin antibody TUJ1 (R&D Systems), followed by an additional 5 washes in PBS for 1 h each. The explants were then incubated overnight in the secondary antibody Alexa Fluor 488-conjugated goat anti-mouse IgG (1:1,000; Molecular Probes), washed 5 times in PBS for 1 h each, and photographed with an AxioCam HRm (Zeiss) camera on a Zeiss Imager Z1 fluorescence microscope.

Quantification of Explant Asymmetry and Total Outgrowth. By manually applying an appropriate intensity threshold to each image and discounting the region encompassing the explant tissue (using Adobe Photoshop), an estimate of the distribution of neurites in each image was obtained as in ref. 26. Outgrowth asymmetry was quantified by using the guidance ratio $GR = (H - L)/(H + L)$, H and L being the number of neurite pixels on the high and low ligand concentration sides of the explant, respectively.

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