Using theoretical models to analyse neural development

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Abstract | The development of the nervous system is an extremely complex and dynamic process. Through the continuous interplay of genetic information and changing intra- and extracellular environments, the nervous system constructs itself from precursor cells that divide and form neurons, which migrate, differentiate and establish synaptic connections. Our understanding of neural development can be greatly assisted by mathematical and computational modelling, because it allows us to bridge the gap between system-level dynamics and the lower level cellular and molecular processes. This Review shows the potential of theoretical models to examine many aspects of neural development.

Morphogens
Secreted factors that can induce different cell fates across a sheet of cells in a concentration-dependent manner by forming gradients.

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The recent growth of knowledge about all aspects of neural development has been immense and has included information on the roles of morphogens in early development, the molecular cues underlying axon guidance and the molecular mechanisms involved in neuronal morphogenesis and synapse formation (BOX 1). Mathematical and computational models can provide insight into how the concerted actions of these molecular and cellular processes lead to the formation of the nervous system (BOX 2). In addition to providing quantitative information (such as calculating the smallest concentration gradient of a guidance cue that a migrating axon might be able to sense[1]), theoretical models provide the unique opportunity to deduce the potential consequences of the multitude of interactions that take place at molecular, cellular and network levels, and thus to help researchers to discover the principles by which the nervous system emerges. The growth in empirical data has facilitated the creation of theoretical models of neural development that are more strongly based on biological processes, yielding predictions that can be tested experimentally.

This Review gives a broad overview of contemporary models of the various stages of neural development, from neural tube formation to the generation of synaptically connected networks. The models described have been chosen to illustrate and contrast the different approaches taken in modelling development, to indicate the insights and predictions that can be derived from these model studies, and to highlight the opportunities and challenges for future modelling.

Neural tube formation

During neural tube formation (neurulation), the lateral edges of the neural plate fuse, creating a hollow cylinder inside the embryo, from which the nervous system will form. This process involves cell movement and changes in cell number, shape and adhesion[2,3]. Mathematical models can be used to explore the many reciprocal interactions between intercellular signalling, gene expression and cell differentiation, motion, adhesion and division that take place[3,4]. For example, the regulation of gene transcription controls differential adhesion between cells, affecting cell movement. Cell movement creates new cell contacts, altering intercellular signalling, which in turn affects gene regulation[5,6].

These reciprocal interactions were taken into account in a computational model of neural tube formation[7] (FIG. 1A,B,C). The model incorporated two transcriptional switches: a neuroectodermal switch that regulates the specification of ectoderm into neuroectoderm (neural plate) and a neuronal switch that controls the differentiation of a subset of neuroectoderm cells into neurons. In this model, bone morphogenetic proteins and Sonic hedgehog (SHH), as well as signal transduction triggered by the binding of Delta to Notch, act on these switches. The genetic switches regulate cell adhesion, movement and division. An important insight from the model was that the major types of neurulation that occur in vertebrates and invertebrates do not necessarily require greatly different mechanisms[8]. If cell motion is turned on by the neuroectodermal switch, a closed neural tube is formed (vertebrate primary neurulation). If the rate of cell division is high, ingression of a neural cell mass takes

Lamellipodia
Sheet-like extensions at the edge of a cell that contain a crosslinked F-actin meshwork and are often associated with cell migration.

Convergent extension
The process by which the tissue of an embryo is restructured so that it narrows along one axis and elongates along a perpendicular axis by cellular movement.

place (vertebrate secondary neurulation). If cell motion is controlled by the neuronal switch rather than the neuroectodermal switch, isolated neuroblasts are formed, as occurs in insects[9]. The model also highlighted the profound morphogenetic potential of the interplay between gene expression and cell differentiation on the one hand, and cell shape, motion and adhesion on the other hand (see also REF. 5).

A more advanced, three-dimensional model of neurulation has since been developed that incorporates a realistic description of the mechanical forces at the subcellular, cellular and tissue levels[4] (FIG. 1D). This model simulates morphogenetic movements in three dimensions, closely matching those that take place in real embryos, and allows for testing of hypotheses about the forces that drive neurulation. For example, experimental studies[10] have shown that the action of lamellipodia on neural plate cells is important for convergent extension of the neural plate before folding. The model showed that normal neurulation does not occur if lamellipodium forces are uniform across the width of the neural plate, thus indicating locations at which differential gene expression might be occurring[10]. Although the model also includes mechanical forces regulated by genes and signalling pathways, it has not yet explored the full dynamical and reciprocal interactions between gene regulation, cell motion and morphogen gradients.

Box 1 | **Stages of neural development**

Neural development begins when, in response to diffusible proteins secreted by the mesoderm, a portion of ectoderm on the dorsal surface of the embryo becomes specified as neuroectoderm. The lateral edges of this one-cell thick sheet of cells (neural plate) elevate, appose each other and then fuse to form a hollow cylinder (neural tube formation), which later develops into the brain and most of the spinal cord. The neural tube at more posterior levels of the future spine is formed by ingression of a mass of neuroectoderm cells, followed by canalization. As a result of molecular gradients, the neural tube subsequently becomes specified into a number of distinct domains (regionalization of the neural tube), the precursors of the different areas of the central nervous system. Next, the wall of the neural tube thickens as new neurons are generated (cell proliferation) and migrate away from the proliferation zone, at the inside surface of the tube, towards the outer surface of the tube (cell migration). Neurons also migrate tangentially (parallel to the surface of the tube). In some regions, migration gives rise to layered structures, as in the cerebral cortex. In the developing retina, tangential cell movements help to create regular spacing of cells (retinal mosaics). During migration, in response to both intrinsic and extrinsic factors, neurons gradually become specified into different cellular types (cell differentiation). Large numbers of neurons die during proliferation and migration. Upon arrival at their destination, neurons begin to produce several undifferentiated neurites. In a competitive process, one of these becomes specified as the axon, whereas those that remain differentiate into dendrites (axon specification). The dynamic behaviour of growth cones causes dendrites to branch extensively and to gradually form their characteristic morphologies (neurite elongation and branching). Guided by diffusible and membrane-bound chemical cues in their environment, axons continue growing to their targets (axon guidance). Once they have arrived in their target region, axons may branch considerably before terminating to form initial synaptic connections with target structures (network formation). Refinement of these connections occurs by retraction of axonal branches that project to the wrong targets and elaboration of branches that project to the correct targets, a process that involves competition for target-derived neurotrophic factors (synaptic competition). The formation and deletion of synapses, outgrowth and retraction of axons and dendrites (structural plasticity), and changes in the efficacies of existing synapses (synaptic plasticity), lead to changes in the connection strength between neurons. Remodelling of axonal arborizations, as well as axon guidance cues, also underlies the formation of topographic maps (topographic map formation). Both establishment and refinement of connectivity are influenced by neuronal activity (for more detailed accounts of neural development, see REFS 169–171).

Regionalization of the neural tube

In the next stage of development, the neural tube becomes specified along its rostrocaudal and dorsoventral axes into distinct domains from which different neural cell types will emerge. A central question is therefore how an apparently spatially uniform neural tube is transformed into a spatially non-uniform structure, with different areas committed to different fates. It is known that, in general, diffusion of a morphogen from its source creates a smoothly declining concentration gradient. This can result in a pattern of cell fates when different morphogen concentrations turn on or off different sets of genes. This plays a part, for example, in the dorsoventral patterning of the neural tube by SHH[11] and the rostrocaudal patterning by fibroblast growth factors (FGFs)[12]. Theoretical models have been used to enhance our understanding of this process in several ways.

One modelling study[13] showed that diffusion of a morphogen from its source together with binding of the morphogen to membrane receptors creates, at steady-state, an even concentration of receptor-bound morphogens across the neural tube. Thus, the study suggested that in addition to simple passive diffusion, intracellular transport mechanisms might be needed to establish a reliable concentration-based positional signalling system. Morphogen transport and signalling can be regulated by non-specific binding to cell-surface molecules, by intracellular trafficking and by complex feedback loops involving up- and downregulation of morphogens and their receptors[14–17]. Future modelling studies could provide insights into the synergistic contributions of each of these elements to tissue patterning.

Hypotheses for how morphogens organize tissues typically consider the morphogen gradient after it has reached a steady state. However, a recent computational model[18] showed that the dynamics of gradient formation are also important for the dorsoventral patterning of the neural tube (FIG. 2). This model incorporated SHH transport and signalling — including free diffusion, binding to cell surface and extracellular matrix components, intracellular trafficking, upregulation of SHH receptor synthesis by SHH, and SHH receptor-mediated degradation of SHH. Using these processes, the model simulated the generation of a sharp boundary between cells fated to become interneurons and motor neurons. Furthermore, it showed that the generation of this boundary relies on both the bistability of the intracellular SHH signalling pathway, and the spatial effects of receptor upregulation and receptor-mediated degradation of SHH. The simulation also predicted, perhaps counter-intuitively, that slowing the transport of SHH can increase its signalling range (see also REF. 17), which supports experimental findings in which modified SHH with altered diffusivity was used[19]. Interestingly, the simulation results showed that a fixed cell-fate boundary is established long before the SHH gradient has stabilized, which can account for

Box 2 | **Classification of models**

There are several ways in which models of biological processes can be classified.

Formal or informal models

Informal models are expressed in words or diagrams, whereas formal models — which this Review is concerned with — are described in mathematical equations or computer instructions[172]. Using formal language forces a model to be precise and self-consistent. The process of constructing a formal model can therefore identify inconsistencies, hidden assumptions and missing pieces of experimental data[173]. Formal models allow us to deduce the consequences of the postulated interactions among the components of a given system, and thus to test the plausibility of hypothetical mechanisms[165]. Models can generate new hypotheses and make testable predictions, thereby guiding further experimental research. Equally importantly, models can explain and integrate existing data[165].

Phenomenological or mechanistic models

Most formal models lie on a continuum between two extreme categories: phenomenological and mechanistic[132,174]. A phenomenological model attempts to replicate the experimental data without requiring the variables, parameters and mathematical relationships in the model to have any direct correspondence in the underlying biology. In a mechanistic model, the mathematical equations directly represent biological elements and their actions. Solving the equations then shows how the system behaves. We understand which processes in the model are mechanistically responsible for the observed behaviour, the variables and parameters have a direct biological meaning and the model lends itself better to testing hypotheses and making predictions.

Although mechanistic models are often considered superior, both types of model can be informative. For example, a phenomenological model can be useful as a forerunner to a more mechanistic model in which the variables are given explicit biological interpretations. This is particularly important considering that a complete mechanistic model may be difficult to construct because of the great amount of information it should incorporate. Mechanistic models therefore often focus on exploring the consequences of a selected set of processes, or try to capture the essential aspects of the mechanisms, with a more abstract reference to underlying biological processes.

Top-down or bottom-up models

Formal models can be constructed using a top-down or a bottom-up approach[174,175]. In a top-down approach, a model is created that contains the elements and interactions that enable it to have specific behaviours or properties. In a bottom-up approach, instead of starting with a pre-described, desired behaviour, the properties that arise from the interactions among the elements of the model are investigated. Although it is a strategy and not a type of model, the top-down approach resembles phenomenological modelling because it is generally easier to generate the desired behaviour without all of the elements of the model having a clear biological interpretation. Conversely, the bottom-up approach is related to mechanistic modelling, as it is usual to start with model elements that have a biological meaning. Both approaches have their strengths and weaknesses.

recent experimental results showing that the dynamics of concentration gradient formation, rather than the steady-state morphogen gradient, seem to play a crucial part in tissue patterning[20]. This model could be used to clarify the many regulatory mechanisms involved in SHH gradient formation and cell fate specification, and to explore the effects of cell division and cell death during patterning.

Proliferation, migration and differentiation

As the wall of the neural tube thickens, cells migrate away from the proliferation zone and become specified into different types of neuron. Few models for these stages of development exist. However, modelling could help us to understand the consequences of the many, simultaneous regulatory interactions that control proliferation, migration and differentiation. These include signals from within a cell, such as the proteins inherited from its precursors, and signals from outside the cell, such as diffusible molecules and membrane-bound molecules provided by other cells.

One of the few models of proliferation[21] considered feedback regulation of proliferation in the context of neurogenesis in the olfactory epithelium. Olfactory receptor neurons derive from a multistage lineage with three proliferating, progenitor cell stages. The model uses differential equations to describe the population sizes of the different cell stages, and incorporates negative feedback from each cell stage on the proliferation of its precursors. One of the findings of this model was that autoregulation of the proliferation of progenitor cell stages and a low death rate of the differentiated cell type enhance the stability of the number of cells in the system. In general, feedback regulation by postmitotic neurons onto earlier stages enables a tissue to control the total cell number and the proportions of differentiated cell types[22].

The layers of the cortex develop in an inside-out manner, with neurons of the deeper cortical layers being generated before those of the superficial layers. By what mechanisms does this inside-out order arise? A model[23] of cell proliferation and migration showed that even a simple set of local instructions inside each cell, together with mechanical interactions between cells, is capable of producing the inside-out lamination of the cortex (FIG. 3A).

Cell migration has also been studied in models of the formation of retinal mosaics, the regularly spaced configuration of retinal cells that emerges from a random pattern during development (reviewed in REF. 24). One of these models[25] showed that regular distributions arise if the tangential movements of retinal neurons are driven by repulsive interactions between neighbouring dendrites. In the model, the cell's dendrites are represented by a circular field around its cell body (a similar approach was taken in REF. 26), and overlap between the fields of neighbouring cells causes cell movement. A second model[27] incorporated a biophysical description of the mechanical forces on the dendrite's cytoskeleton caused by dendritic interactions, and suggested that the rigid components in the cytoskeleton play a key part in the formation of retinal mosaics.

An important mechanism for cell differentiation (and for pattern formation in general[28,29]) is lateral inhibition, whereby initially undifferentiated cells compete with their neighbours to acquire a particular cell fate. A major pathway by which lateral inhibition is mediated and a wide range of patterns is produced is the Delta–Notch signalling system[30–32] (FIG. 3B). Another model of retinal mosaic formation[33] predicted that Delta–Notch signalling alone is insufficient to produce mosaics of the same regularity as those observed experimentally, and that additional processes such as lateral cell movement or cell death are required.

An important challenge in modelling the early stages of neural development is to take into account the links between proliferation, migration and differentiation[34]. This was achieved in a phenomenological model (BOX 2) of neocortical growth[35]. It is also important to couple proliferation, migration and differentiation to intracellular

Delta–Notch signalling
Signalling pathway involved in cell–cell communication and cell differentiation. Because both the ligand Delta and the receptor Notch are membrane-bound proteins, cells must be adjacent for signalling to occur.

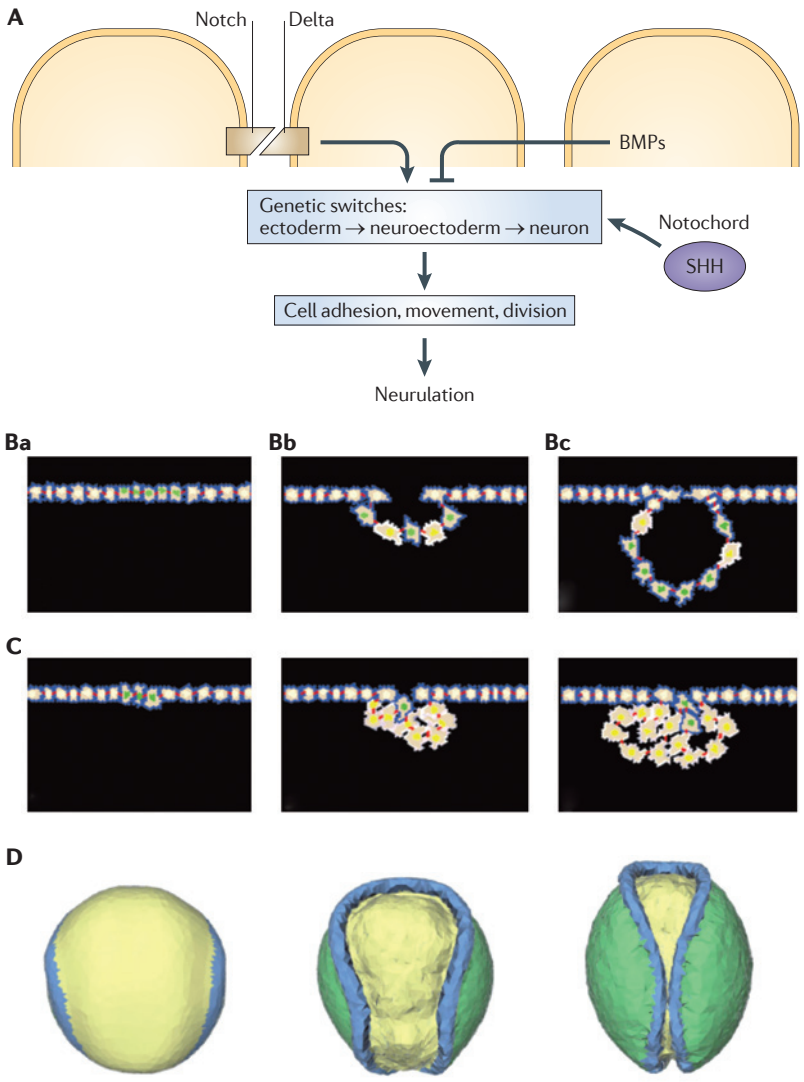

Figure 1 | **Modelling neural tube formation. A** | A computational model of neural tube formation[7] contains genetic switches that regulate the specification of ectoderm into neuroectoderm (neural plate) and the differentiation of neuroectoderm cells into neurons. Bone morphogenetic proteins (BMPs), Sonic hedgehog (SHH) and signal transduction triggered by the binding of Delta to Notch, act on these switches. The genetic switches, in turn, regulate cell adhesion, movement and division. **B** | The model showed how interactions between gene expression, intercellular signalling, and cell division and motion can lead to neural tube formation. The dorsal part of a transverse embryonic section is shown at successive times. **Ba** | Before invagination, the nuclei of cells expressing the neural plate gene Notch (shown in green) are observed in the area that will become the neural plate. Attachment points between cells are shown in red. **Bb** | Neural plate cells express Notch alone, or Notch together with the neuronal gene Delta (shown in yellow). Cell membranes are shown in shades of blue, and lighter colours indicate larger concentrations of Delta. The neural plate starts invaginating while epithelial cells grow over the neural cells, forming the neural 'folds'. **Bc** | Neural tube formation as a result of the joint effect of neural cells migrating downwards and epithelial cells dividing and pushing the neural folds inwards. **C** | If the model is tested under conditions of high cell division, ingression of a Delta- and Notch-expressing neural cell mass takes place (resembling the initial stage of secondary neurulation). **D** | A more advanced, three-dimensional model of neurulation[4] incorporates a detailed description of the mechanical forces at the subcellular, cellular and tissue levels. The model produces morphogenetic movements closely matching those of the developmental stages of axolotl neurulation. The neural plate is shown in yellow, neural folds are shown in blue and non-neural ectoderm is shown in green. Parts **B** and **C** are modified, with permission, from REF 7 © (1998) Wiley. Part **D** is reproduced, with permission, from REF 4 © (2008) IOP Science.

gene regulatory networks[36,37]. A recent model[38] of the differentiation of the neocortex into different areas along the anterior–posterior axis predicted which of the possible regulatory networks of gene interactions can reproduce the anterior–posterior gene expression pattern observed experimentally. The model suggested that a regulatory network previously proposed on the basis of experimental observations[39] cannot explain the experimental data.

During development, the cellular environment changes, resulting in changes in gene expression that drive processes such as differentiation and migration. In turn, these processes change the cells' environment. New simulation tools, such as CX3D[23] and CompuCell[40], will be helpful in studying the consequences of these reciprocal interactions. CX3D is a tool for modelling all stages of corticogenesis, such as cell division and migration, and the influence on these processes of mechanical forces, cell–cell contact and diffusible signals. CompuCell models the morphogenesis of multicellular organisms, in particular simulating the interaction of gene regulatory networks with cellular mechanisms such as cell adhesion, division, differentiation and migration. Furthermore, as recent evidence shows that even early developmental processes, such as proliferation, migration and differentiation, can be regulated by electrical signalling[41], future models of these processes would need to take this into account.

Axon–dendrite differentiation

During or after migration, neurons begin to project a number of extensions, one of which differentiates into the axon, whereas those that remain become dendrites. Axon specification seems to involve competitive interactions among the undifferentiated neurites, with the neurite that is slightly longer than the others tending to become the axon[42].

How does a single axon among neurites of equal potential become specified? Only a few model studies have addressed this question. One of these[43] studies modelled the transport of an unspecified growth-promoting chemical from the soma to the growth cones at a rate that was assumed to increase with the neurite's growth rate. The model showed that this positive feedback loop results in a single, rapidly growing axon if one neurite has a slightly larger initial length. Subsequent experimental work proposed that signalling molecules regulating protein trafficking and the behaviour of the cytoskeleton might form such positive feedback loops[44,45]. Because of its dependence on levels of intracellular calcium, axon specification might also be regulated by electrical signalling[46,47].

Future modelling studies of axon specification should incorporate data on the intracellular signalling pathways involved in axon–dendrite differentiation[48,49], and investigate whether the interactions between these identified cellular and molecular mechanisms can give rise to the feedback loops necessary for the establishment of neuronal polarity[50]. Recently it was observed that shootin 1, a key regulator of axon outgrowth, accumulates in neurite tips in a neurite length-dependent manner[51]. In

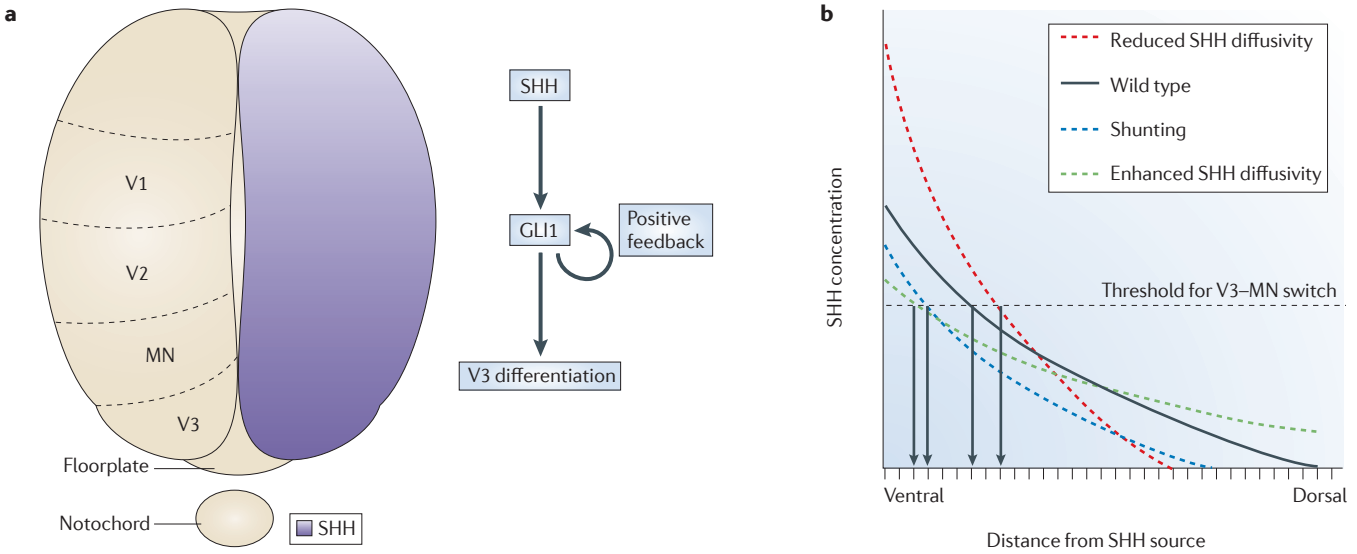

Figure 2 | **Modelling the dorsoventral regionalization of the neural tube.** A computational model[18] has been used to study the specification of V3 interneurons (V1–V3 are distinct populations of ventral interneurons) and motoneurons (MNs) under the influence of Sonic hedgehog (SHH) secreted from the floorplate. **a** | A schematic transverse cross section of the neural tube. Labels on the left side of the tube indicate mature cell fates that will emerge from each region. SHH secreted by the floorplate diffuses through the neural tube and the concentration of SHH determines the fate of cells. SHH stimulates intracellular GLI1 expression, which in turn induces differentiation into V3 interneurons. As SHH concentration rises above a threshold concentration, it stimulates GLI1 production to the point at which GLI1 positively feeds back on its own expression. The on–off GLI1 expression interface demarcates the V3–MN boundary. **b** | The model predicted how three types of mechanisms that affect SHH transport modify the SHH extracellular gradient and shift the position of the V3–MN boundary. Reducing SHH diffusivity, which causes accumulation of SHH near its source, can, paradoxically, increase the signalling range of SHH, leading to a dorsal shift in the V3–MN boundary. Conversely, enhancing SHH diffusivity can lead to a ventral shift in the boundary. Sequestering of free SHH by transmembrane proteins (shunting) decreases SHH over the entire tissue, shifting the boundary ventrally. Part **b** is modified, with permission, from REF 18 © (2006) The Company of Biologists.

combined experimental and modelling work[51] (FIG. 4a,b), it was shown that anterograde transport and retrograde diffusion can account for this, and that length-dependent accumulation, together with shootin 1-dependent neurite outgrowth[52], constitutes a positive feedback loop that can amplify stochastic fluctuations in shootin 1, thereby generating an asymmetric signal for axon specification.

Neurite elongation and branching

Dendritic development is driven by complex interactions between intrinsic molecular pathways and local environmental signals[53–56]. Although many of the molecules involved have been characterized, we are still far from a mechanistic understanding of dendritic morphogenesis. A central question is how neuron type-specific dendritic morphologies, in terms of size and branching patterns, emerge from underlying intracellular signalling cascades and extracellular influences.

To shed light on possible growth mechanisms, some models[57–59] have created virtual dendritic trees using branches with morphological characteristics that are sampled from distributions derived from real neurons. These models have indicated, for example, that the centrifugal order of a dendritic segment may determine the probability of branching in most cell types, except in pyramidal cell apical trees, where this probability seems to depend more on path distance from the soma[58].

Centrifugal order
The distance of an axonal or dendritic segment from the soma, in terms of the number of branch points between the segment and the soma.

The stochastic phenomenological models of Van Pelt[60–62] describe the growth of a neuron over time, from the perspective of individual growth cones (FIG. 5a,b). By two actions of the growth cone — elongating the trailing neurite or branching into two daughter growth cones — the whole dendritic tree is gradually created over time. These models are capable of accurately producing the morphology and variability in the morphology of a wide range of neuron types, and have predicted interesting growth differences between cell types, such as the degree of competition between growth cones[60]. These models form the basis of the recently developed simulation tool NETMORPH[63] for the stochastic generation of large-scale neuronal networks with realistic neuron morphologies.

The models of Van Pelt also indicated that the probability of branching may be modulated by the total number and centrifugal order of terminals, but they do not identify the underlying biophysical mechanisms. A more recent mechanistic model[64] (BOX 2), in which branching depends on a substance (such as tubulin or microtubule-associated proteins (MAPs)) that is produced in the cell body and transported to the terminals, showed that the same modulation of branching can emerge as a result of transport-limited effects.

A number of models have explored the implications of tubulin dynamics for neurite outgrowth. In one of

Compartmental-based models
A modelling approach in which a spatially continuous structure, such as a neurite, is divided into a large number of small compartments. Each compartment is assumed to be a homogeneous entity, and neighbouring compartments interact chemically or electrically.

these[65], tubulin is produced in the cell body and transported by diffusion and active transport to the growth cones, where assembly in microtubules elongates the neurite. The model showed that the fastest growing neurite branch, by creating a steep concentration gradient and thus attracting most of the tubulin, can prevent the outgrowth of other branches. Stopping the growth of the fastest branch 'awakens' the other branches. Such competitive outgrowth of neurite branches was subsequently supported experimentally[66,67]. This tubulin-based model has been extended in compartmental-based models[68,69] (FIG. 5c) that incorporate neurite branching, modulation of neurite elongation and branching by MAPs, and calcium dynamics (reviewed in REF. 70). These models produce a wide variety of characteristic dendritic trees (FIG. 5d) depending on the calcium-dependent rates of phosphorylation and dephosphorylation of MAPs, and predict differences in these rates in neurons with different branching patterns.

Another model of neurite outgrowth is based on membrane expansion by exocytosis of vesicles transported inside the cell body and neurite[71]. Microtubules stabilize neurites by decreasing the rate of endocytosis and guide vesicle movement. Depending on the coupling between microtubules and vesicle dynamics, the model predicted three different growth modes: steady 'axonal' growth, stochastic 'dendritic' growth and fast oscillatory growth.

The mechanistic models previously described consider the internal mechanisms that govern neurite elongation and branching. However, other models focus mainly on external influences. For example, to better understand the role of growth cone-generated mechanical tension in axon elongation, a model was developed[72] that incorporates cell adhesion between axon and substrate. Experimental observations have shown that axons elongate by stretching or by addition of new material at the tip, and the simulations predicted that this depends on the strength of adhesion along the axon and on its viscosity.

Another model[73] focuses on the role of the tension that filopodia exert on the growth cone. Growth cone filopodia attach to fixed, randomly dispersed adhesion sites in the environment, and neurite branching is induced if the forces pulling the growth cone apart overcome a certain threshold. The model can account for some empirically observed morphological characteristics of dendritic trees, such as centrifugal order-dependent segment lengths.

The growth of dendritic trees based on diffusion-limited aggregation has been proposed by the creators of another model[74]. Although the model was able to generate diverse neuronal shapes by changing the space available for growth and the spatial distribution of particles needed for growth in the environment, a direct translation to biological processes is difficult, as real neurites do not directly grow by aggregating particles from their environment.

Repulsive interactions between dendrites may underlie the development of dendritic trees that uniformly cover space[75], such as those of retinal ganglion cells and Purkinje cells. A model study[76] showed that such dendritic patterns can emerge autonomously if two hypothetical chemicals, an activator and a suppressor, control dendrite outgrowth. Outgrowth is catalysed by the activator, which diffuses only intracellularly, and is inhibited by the activator-induced suppressor, which is secreted and diffuses extracellularly, causing repulsion between dendrites. However, it is not clear what the nature of the chemicals might be *in vivo* and whether this approach can be extended to describe the development of other types of neuron.

Finally, a number of theoretical studies have explored whether dendritic branching patterns can be understood as optimizing functional constraints, which may

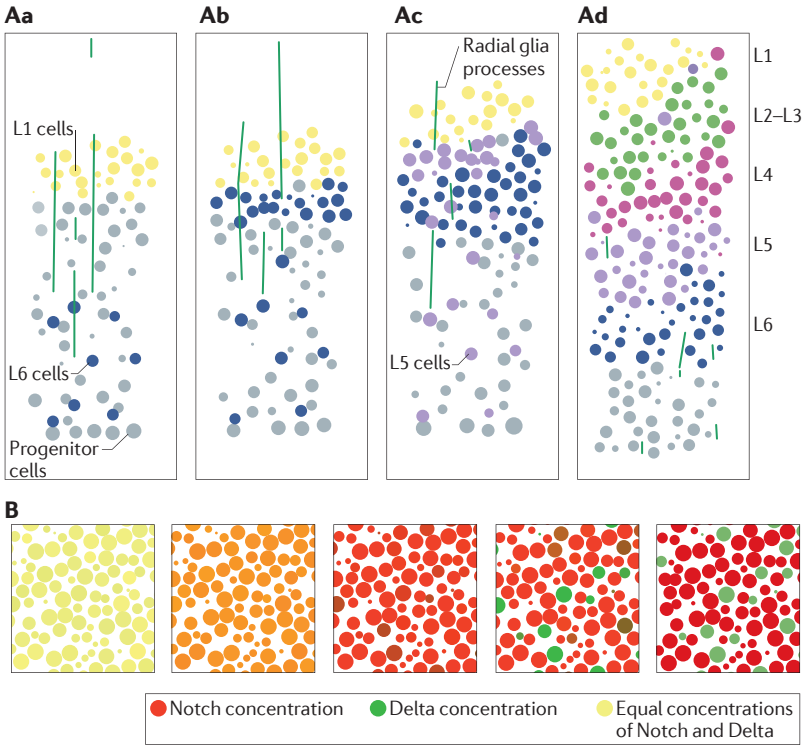

Figure 3 | **Modelling cell proliferation, migration and differentiation. A** | During development of the cortex, cells of the deeper cortical layers are generated before those of the superficial layers. A computational model[23] showed that a simple set of cellular instructions can produce this inside-out order of cortical development. In the model, neuron precursors were instructed to behave according to the following rules: they move randomly until they touch a radial fibre on which they fix themselves, they migrate distally along the fibre, leave the fibre and stop migration when they encounter a layer 1 (L1) cell. **Aa** | L6 neuron precursors are produced by asymmetrical division of the progenitor cells. They migrate along radial glial processes. **Ab** | When the neuron precursors detect the top-most L1 cells, they stop migrating by detaching from the radial fibres. Owing to the mechanical interactions between cells, L1 is pushed upwards. **Ac** | When L5 neurons are produced, they follow the same path, passing through L6 cells until they contact L1, progressively pushing L1 upwards. **Ad** | The same process occurs for L4 and L2–L3. A few cells end up in the wrong layer, as observed in the cortex[176]. **B** | Computational models have also been used to study the mechanisms by which cells can acquire different fates. One such model of cell differentiation starts with a homogeneous population of cells expressing equal concentrations of the membrane-bound ligand Delta and its receptor Notch[23,30]. Each cell activates Notch in its neighbouring cells, depending on its own Delta level, while decreasing its own Delta concentration based on its Notch level. Over time, this results in populations of cells with high Notch or high Delta levels. Figure is reproduced, with permission, from REF 23 © (2009) Frontiers Research Foundation.

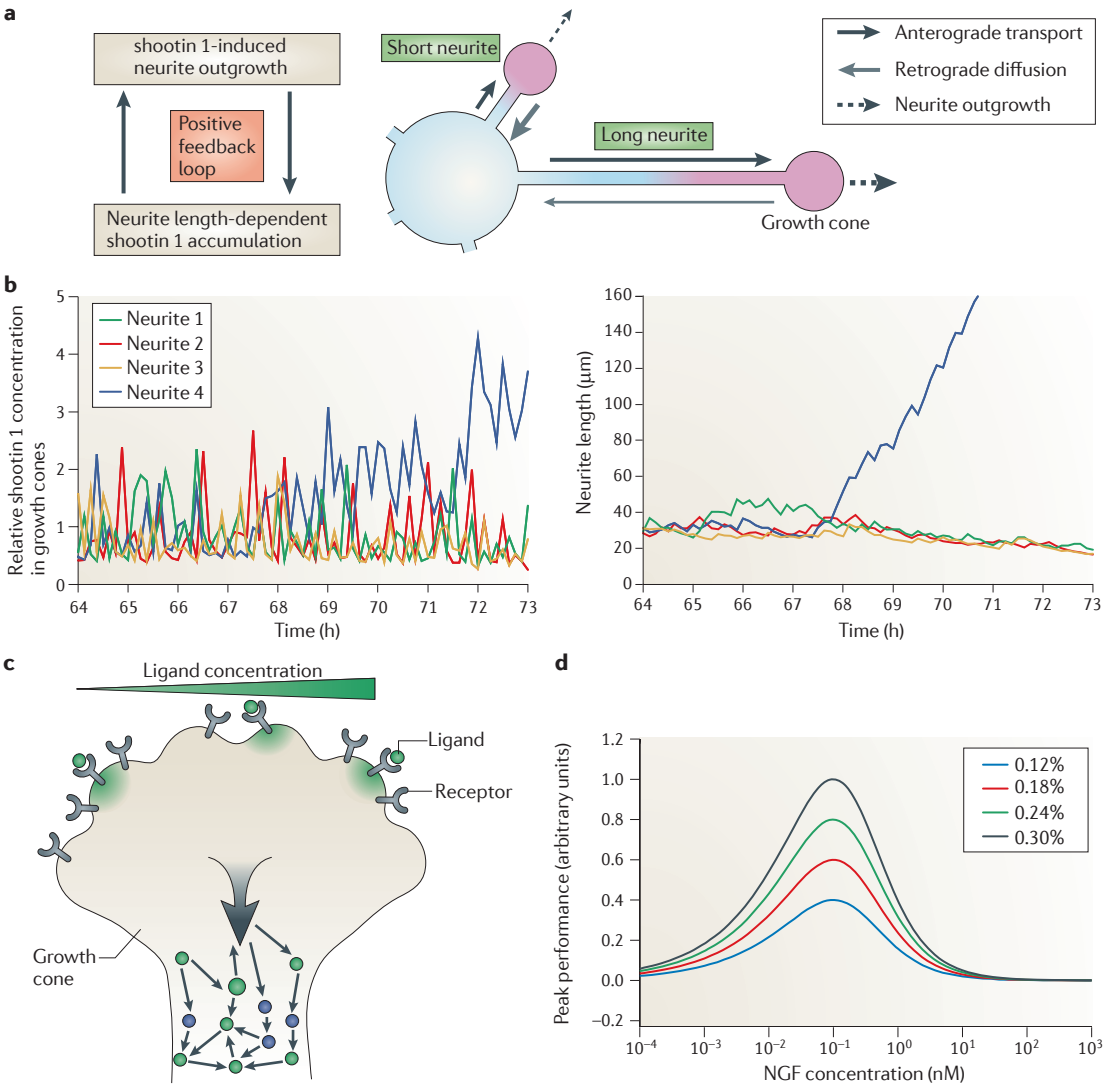

Figure 4 | **Modelling axon–dendrite differentiation and axon guidance. a** | Theoretical models have been used to analyse how a single, rapidly growing axon could emerge from neurites of equal potential. A model showed how shootin 1, a key regulator of axon outgrowth, accumulates in neurite tips in a length-dependent manner[51], and how the dynamics of shootin 1 causes one neurite from a group of neurites of similar length to outgrow its siblings and become the axon. Shootin 1 is in a stochastic manner actively transported from the cell body to the growth cone, from where it diffuses back to the cell body. This leads to preferential accumulation of shootin 1 in long neurites, because retrograde diffusion, but not active anterograde transport, becomes weaker with length. The strength of anterograde transport and retrograde diffusion is indicated by the thickness of the arrows. At the growth cone, shootin 1 induces outgrowth[52]. This therefore results in a positive feedback loop that amplifies small stochastic fluctuations in shootin 1. **b** | Shootin 1 accumulation and neurite length fluctuate stochastically until one neurite predominately accumulates shootin 1 and undergoes rapid outgrowth. A similar course of events was observed experimentally[51]. **c** | Theoretical models can also be used to understand the mechanisms by which an axonal growth cone 'reads' extracellular gradients of guidance molecules and translates this into growth cone turning. A Bayesian model[84] of axon guidance showed that a growth cone with 'noisy' receptors (receptors on which ligand binding fluctuates) can most reliably estimate the direction of an external ligand gradient if it assigns more weight to the signals from bound receptors that are further away from the growth cone's centre. This is the optimal rule for deciding what the direction of the gradient is. A schematic growth cone is shown in an external concentration gradient of ligand molecules. Ligand molecules bind probabilistically to receptors. Signals from bound receptors are then combined to decide the most consistent gradient direction for that pattern of ligand binding. **d** | The model with this optimal decision rule was used to predict — for different gradient steepnesses and concentrations of the ligand nerve growth factor (NGF) — the performance of the growth cone in estimating the correct gradient direction. The percentages refer to the fractional change in concentration across 10 μm. The performance is better at higher gradient steepness and drops off faster at higher than at lower ligand concentrations. Furthermore, the width of the curve increases with gradient steepness. The performance of real growth cones was found to show the same relationship with gradient steepness and ligand concentration[84], suggesting that real growth cones might employ such an optimal decision rule. Parts **a** and **b** are reproduced, with permission, from REF 51 © (2010) Macmillan Publishers Ltd. All rights reserved. Parts **c** and **d** are reproduced, with permission, from REF 84 © (2009) National Academy of Sciences.

Diffusion-limited aggregation
The process whereby particles undergoing random movements cluster together to form aggregates.

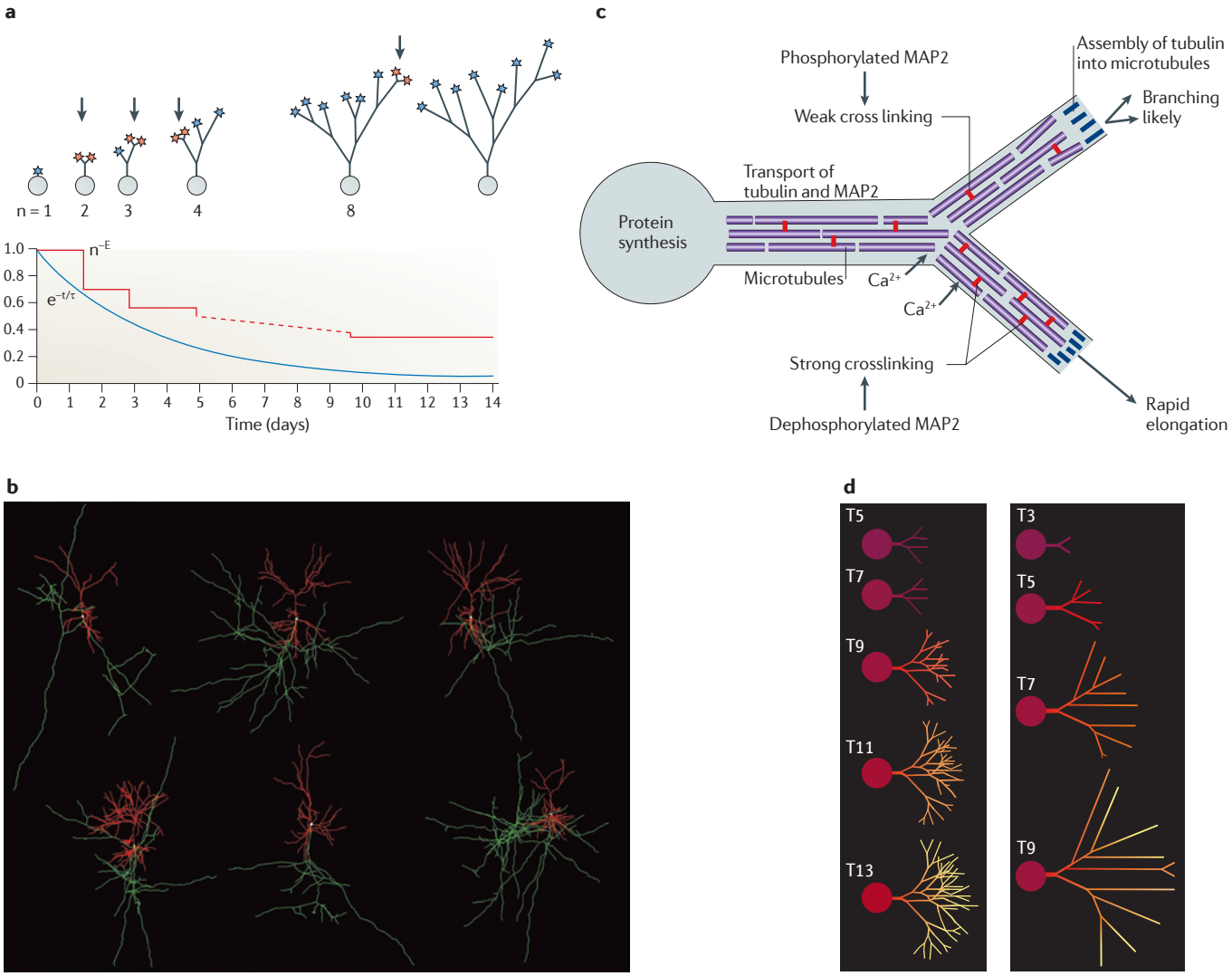

Figure 5 | **Modelling neurite elongation and branching.** An important question is how the morphology of axonal and dendritic trees is determined. Theoretical models have provided insight into the possible mechanisms through which branching patterns are controlled. **a** | In a phenomenological model of neurite outgrowth[60-62], each neurite starts with an initial segment with a growth cone at the tip. The growth cone elongates the neurite and can branch, creating two daughter growth cones (branching events are shown by an arrow and red growth cones). Each growth cone in the growing tree has a branching probability that is the product of three factors: a factor that decreases with developmental time (shown by a blue line), a factor that changes with the growth cone's centrifugal order (not shown) and a factor that decreases with the momentary number (n) of growth cones in the tree (shown by a red line). This last factor reflects competition between growth cones for resources. Parameter E denotes the strength of competition. After each branching event, the branching probability thus decreases. In this example, E = 0.5 and τ = 3.7 days. **b** | Six model-generated neurons[177]. The model parameters, such as competition strength, were chosen so that the morphology of the generated trees best matched the morphology of layer 2–3 rat cortical pyramidal neurons. Axons are shown in green and dendrites are shown in red. **c** | In a biophysical model of neurite outgrowth[68], tubulin is produced in the cell body and transported by diffusion and active transport to the growth cones, where assembly in microtubules elongates the neurite. Neurite outgrowth is further modulated by microtubule-associated proteins (MAPs), with phosphorylated MAP2 favouring branching (as a result of weak crosslinking of microtuble bundles by phosphorylated MAPs) and dephosphorylated MAP2 favouring elongation (as a result of strong crosslinking)[178]. Phosphorylation and dephosphorylation increase with the intracellular calcium concentration. Calcium enters along the whole neurite and diffuses inside the cell. **d** | Depending on the relative rates of calcium-dependent MAP phosphorylation and dephosphorylation, and in interaction with the calcium dynamics, the model produces a variety of characteristic dendritic trees. The results of two parameter settings are shown. If phosphorylation reaches its half-maximum rate at a higher calcium concentration than dephosphorylation, dendrites are produced in which branching increases distally (left side). If dephosphorylation reaches its half-maximum rate at a higher calcium concentration than phosphorylation, trees with elongated distal dendrites are generated (right side). High calcium concentration is shown in yellow. T, developmental time. Part **b** is reproduced, with permission, from REF 177 © (2010) Frontiers Research Foundation. Part **c** is reproduced, with permission, from REF 70 © (2006) BioMed Central. Part **d** is modified, with permission, from REF 68 © (2001) Elsevier.

give insight into developmental principles as well. For example, the branching structure of Purkinje cells can be well simulated by models designed to minimize the path length from synapses to soma while constraining total dendritic length[77,78]. Likewise, the total dendritic size of pyramidal cells seems to be homeostatically conserved[79].

We are still far from understanding how the concerted actions of intracellular molecular mechanisms and extracellular signals can generate the characteristic branching patterns of the different types of neuron. Axonal and dendritic growth is also known to be affected by electrical activity and synapse formation[56,80,81]. These effects have not yet been incorporated in models. Because of the widely different timescales, including the effect of electrical activity on the developmental process may require an adaptive modelling approach in which the model can switch from simulating development to the simulation of short periods of activity.

Axon guidance

A key process in the guidance of axons to their targets is chemotaxis, whereby growth cones detect and follow gradients of target-derived diffusible molecules or molecules bound to the extracellular matrix or to other cells. Although recent work has uncovered many of the molecules that are involved in this process, the mechanisms underlying chemotaxis are still unclear.

A series of related theoretical models address the implications for chemotaxis of the binding of diffusible molecules to their receptors at the growth cone. Growth cones are thought to sense concentration gradients by comparing receptor binding across their spatial extent. Therefore, the noise resulting from fluctuations in receptor binding should not be larger than the spatial difference in receptor binding. One model of the physics of receptor–ligand interactions[1] estimated the smallest gradient in ligand concentration that the growth cone can detect. A further study showed that the experimentally observed decline in gradient detection on either side of an optimal ligand concentration[82] can be quantitatively reproduced in an extended model[83] that also includes spatial and temporal averaging of the binding state of receptors. A Bayesian ideal observer of gradient detection by growth cones was developed in another model[84] that is also based on the hypothesis that a principal constraint on gradient detection is intrinsic receptor binding noise (FIG. 4c,d). This model predicted how the response of an axon should vary with gradient steepness and absolute concentration. This prediction was confirmed[84] in an experimental study that revealed the degree of sensitivity of the growth cone to gradients of ligand molecules to be much higher than previously reported[82].

More detailed models have also taken into account filopodial dynamics. A filopodium-based model for axon guidance was developed[85] in which new filopodia are preferentially generated in the region of the growth cone surface where ligand binding is highest (in the case of attraction) or lowest (in the case of repulsion), and the growth cone turns towards the average direction of the filopodia. One prediction of the model, which is not yet tested experimentally, was that the growth cone may display qualitatively different sensitivity curves to attractive and repulsive gradients.

Biochemical events in the cytoplasm underlie the morphological changes in the growth cone during axon guidance. A model based on the RHO GTPase system showed that activation of a cell division cycle 42 (CDC42)-specific guanine nucleotide exchange factor (GEF) results in a switch-like response in the activities of GTPases[86]. This was proposed to constitute the molecular basis for the decision mechanism determining the direction of growth cone expansion.

Challenges for future models of axon guidance include the need to take into account the concerted action of attractive and repulsive cues, the role of contact-mediated versus diffusive cues, adaptation of growth cones to changes in absolute ligand concentration, and changes in sensitivity to cues as axons traverse into another leg of their journey towards their target. These factors can be studied using simulation frameworks for axon guidance[87,88]. For example, the framework in REF. 88 provides a set of mathematical tools for simulating the migration of multiple axons through complex environments that may include any number of sources of membrane-bound or diffusible guidance factors. Inspiration can also be drawn from parallels between axon guidance and chemotaxis in systems such as bacteria, leukocytes and amoebae (*Dictyostelium*) in which mathematical modelling has been fruitful[89].

Network formation

Once they arrive in their target region, axons start to form synaptic connections. This process involves a great deal of structural plasticity, with formation and deletion of synapses, and outgrowth and retraction of axons and dendrites, causing previously unconnected neurons to become connected and vice versa[90–95]. Many forms of structural plasticity are dependent on the neuron's level of electrical activity[41,67,80,81,95–97], and thereby often seem to act to maintain the average electrical activity of the neuron at a particular level (homeostasis)[98]. Some of the models of structural plasticity described below have studied the implications of this homeostatic structural plasticity.

In one model of homeostatic plasticity[26,99–101], the axonal and dendritic processes of each neuron are represented by a single, circular field around its cell body (FIG. 6A). High levels of neuronal activity cause these neuritic fields to contract, and low levels cause them to expand. Several interesting phenomena emerge: the neurons self-organize into a network and go through a transient phase in which synaptic connectivity is much higher than in the final state. The network ultimately reaches global homeostasis of network activity, even though the neurons can monitor only their own activity level. The model predicted, perhaps counter-intuitively, that too much inhibition prevents the normal pruning of exuberant connections and results in a network with high overall connectivity and strongly oscillatory electrical activity. This may clarify experimental findings

Chemotaxis
The phenomenon in which cells or bacteria direct their movement according to gradients of chemicals in their environment.

Bayesian ideal observer
A theoretical observer that uses the concepts of Bayesian statistical decision theory to determine optimal performance in a task, given the available stimulus information.

RHO GTPase system
The group of molecules related to the product of the oncogene *RAS*, which are involved in controlling the polymerization and subsequent organization of actin.

showing that enhanced inhibition during development resulted in epileptic networks in adulthood[102,103]. Furthermore, the model is capable of self repair, automatically generates size differences between the neuritic fields of excitatory and inhibitory cells (although they have identical growth rules), and shows that the developmental course of connectivity and activity in cultures of dissociated cortical cells as well as the formation of

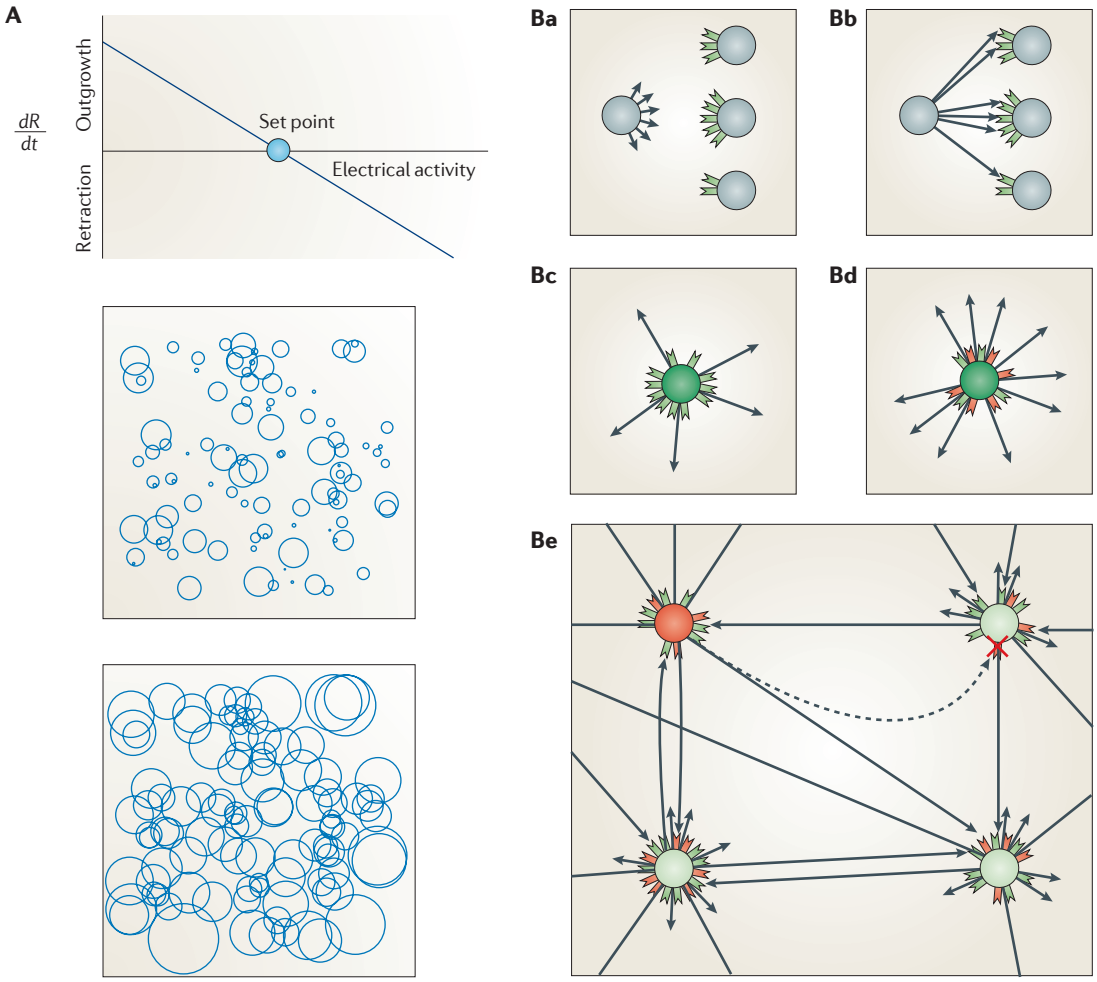

Figure 6 | **Models that investigate the implications of homeostatic structural plasticity for network formation.** Synaptic connectivity exhibits a high degree of plasticity, and synapse formation and deletion often seem to take place in response to changes in a neuron's activity and act to maintain its activity at a particular level. Some theoretical models have been used to study the implications of this homeostatic structural plasticity. **A** | In one model, the neurite size of each neuron is represented by a circular field[99,101]. This field expands when the neuron's activity is below a set level and retracts when it is above this level. Cells connect synaptically when their fields overlap, with the connection strength being proportional to the area of overlap. As neurons with initially randomly sized radii (middle panel) grow, they begin to form more — and stronger — connections, increasing the level of activity in the network. As neurons adjust the size of their neurite fields, they eventually reach equilibrium (bottom panel), in which all radii remain constant and the average activity level of all neurons is at the set level.
Ba | In a model that takes a more detailed approach[107], each neuron has presynaptic elements (shown by arrows) and postsynaptic elements (shown in green and red), representing axonal boutons and dendritic spines, respectively. **Bb** | The pre- and postsynaptic elements merge randomly to form synapses. **Bc** | When neuronal activity is lower than a set value, neurons generate more excitatory postsynaptic elements (elements that can receive connections from excitatory cells are shown in green), thereby enhancing their probability of receiving incoming excitatory connections. **Bd** | When activity is higher than this set value, neurons reduce excitatory postsynaptic elements and increase inhibitory ones (elements that can receive connections from inhibitory cells are shown in red). In this example, activity increases presynaptic elements. **Be** | As the number of presynaptic and postsynaptic elements change according to the level of activity, synaptic connections break and new ones form. The red cross indicates a deleted postsynaptic element, and the dashed arrow shows the corresponding presynaptic element that has retracted and now projects to another neuron. As neurons change their connectivity, the network eventually reaches an equilibrium in which the average activity of all neurons is at their set value. This activity-dependent rewiring of connections can account for the inverse relationship between the rate of cell proliferation and the amount of rewiring in the hippocampal dentate gyrus[107]. Cell bodies of excitatory cells are shown in green, the cell body of the inhibitory cell is red. R, radius of the circular field. Part **A** is reproduced, with permission, from REF 105 © (2007) Elsevier. Part **B** is modified, with permission, from REF 107 © (2008) Wiley.

critical connectivity can be produced by homeostatic structural plasticity[104–106].

In a more detailed model of activity-dependent structural plasticity[107], each neuron has a separate number of presynaptic elements (axonal boutons) and postsynaptic elements (dendritic spines), and synaptic connections are formed by randomly combining pre- and postsynaptic elements, the number of which changes in a homeostatic way as a function of the cell's level of electrical activity (FIG. 6B). Changes in the number of elements may cause an existing synapse to break, but the remaining pre- or postsynaptic element continues to be available for synapse formation. In this way, synaptic connections can be re-routed (synaptic rewiring). The model showed that the inverse relationship between cell proliferation and synaptic rewiring, observed experimentally with the embedding of young neurons in the adult hippocampal dentate gyrus, can arise as the result of the neurons' need for activity homeostasis[107]. The model also predicted which stimulation regimes can most effectively promote network repair after a local cortical lesion or reduction in input[108].

In the models described above, the growth rules of a neuron depend only on the neuron's own level of activity. Another model of structural plasticity has been developed[109] in which the correlation between pre- and postsynaptic activity controls synapse formation and elimination but without explicitly incorporating synaptic rewiring. As in the previous models, the rate of synapse elimination increases with postsynaptic activity, leading to homeostasis of firing rate.

In another model[110] it was shown that correlation-based synaptic rewiring can lead to the formation of small-world connectivity. However, the rewiring rules use information that is not locally available at the neuron, such as its synchrony of firing with neurons to which it is not connected. Models that incorporate (short-term) synaptic rather than structural plasticity also predicted the emergence of particular connectivity structures, such as critical connectivity[111].

Models of structural plasticity so far represent neuronal morphology in a highly abstract manner. Simulation frameworks such as NETMORPH[63] and CX3D[23] grow more realistic neuronal morphologies, but in these models outgrowth and synapse formation are, as yet, independent of electrical activity.

Synaptic competition

During development, cells are initially innervated by more axons than are ultimately maintained in adulthood. In the neuromuscular system, axonal branches are withdrawn until each muscle fibre is innervated by a single motor axon. Similarly, in the visual system, the formation of ocular dominance columns involves retraction of axonal branches. The models described below study competition between innervating axons or synapses (competition models are reviewed in REFS 112,113).

The dual constraint model, which was proposed some years ago[114–116], remains an influential model for the development of mononeuronal innervation in the neuromuscular junction. It combines competition for a postsynaptic resource located in the muscle fibre with competition for a presynaptic resource located in each motor neuron. It offers an explanation for various experimental observations, such as the reduction in motor unit size during development[117] and the occurrence of persistent polyneuronal innervation in partial denervation experiments[118]. The model predicted that axonal branches can retract in the absence of axonal branches from other motor neurons — that is, without competition. There are conflicting experimental results in relation to the possibility of this so-called intrinsic withdrawal[119–122], and it remains to be unequivocally confirmed experimentally. What the pre- and postsynaptic resources in the dual constraint model precisely represent biologically has not been made clear.

Another model of axonal competition[123] is explicitly based on neurotrophins as target-derived resources, and it implements in a fully dynamical way the release and degradation of neurotrophins, the production, insertion and turnover of neurotrophin receptors, the binding of neurotrophins to their receptors at axon terminals, and uptake of bound neurotrophins (FIG. 7A,B). The model predicted that competition requires neurotrophins to upregulate the number of their own receptors. Importantly, this prediction was recently confirmed experimentally by a study showing that neurotrophins promote expression of their own receptors, and that perturbation of this feedback disrupts the dynamics of competition[124]. In the same study, a model was presented that is very similar to the previous one but, in addition to competition for neurotrophic factors, also incorporates direct negative influences between neurons (for other models based on direct negative interactions, see REFS 125,126). Both models[123,124] consider a single postsynaptic neuron with a number of innervating neurons, and need to be extended to a situation in which there are multiple postsynaptic targets — as occurs in the neuromuscular junction, for example. Furthermore, there is no direct role of electrical activity in these models, as in previous less biophysically explicit neurotrophin-based models[127–131] that include activity-dependent release and uptake of neurotrophins to model the development of ocular dominance columns.

Many models[132–136] have shown that ocular dominance and orientation columns can arise through Hebbian learning (steered by spontaneous or sensory-driven activity) complemented by some form of synaptic competition, so that when the synaptic strength of one input grows, the strength of the others shrinks. Whereas many models phenomenologically enforce competition by requiring the total strength of all synapses onto a postsynaptic cell to remain constant (synaptic normalization)[137], others implement putative competitive mechanisms, such as dependence on neurotrophins[127–131] and modified Hebbian learning rules. A Hebbian learning rule model that uses a sliding threshold to determine whether long-term potentiation (LTP) or long-term depression (LTD) occurs[138] produces a variety of receptive fields similar to those seen experimentally, and experimental evidence for this learning rule was subsequently found[139]. More

Critical connectivity
A pattern of connectivity between neurons in which each electrically active neuron causes an average of one other neuron to become active, so that network activity neither dies out nor increases.

Motor unit size
The number of muscle fibres that is contacted by a given motor neuron.

Polyneuronal innervation
In mononeuronal innervation, a target cell is innevervated by just a single neuron; in polyneuronal innervation, by more than one neuron.

Hebbian learning
Synaptic connections between a presynaptic neuron and a postsynaptic neuron are strengthened when their activity is correlated (cells that fire together wire together).

Spike timing-dependent plasticity
Changes in the strength of synapses that depend on the relative timing of the presynaptic and postsynaptic action potentials.

Competitive learning
A learning rule whereby changes in synaptic strength take place only for synapses that impinge on the output cells that respond most strongly to an input.

recent models have shown that spike timing-dependent plasticity (STDP) can also give rise to ocular dominance columns[140] and orientation selectivity[141], and that cortical reorganization following retinal damage can be better explained by STDP than by standard, correlation-based, Hebbian rules[142]. All the models of ocular dominance columns that have been created are able to explain the normal formation of columns, but no single model can yet explain all the experimental data, including the effects of various experimental manipulations[134]. The more abstract models, based on competitive learning, seem to do best in accounting for most experimental findings[132,143–145]. Important challenges for future modelling studies are to translate these abstract models in more biologically based models and to help to elucidate the contribution and interaction of molecular cues[146], spontaneous activity and sensory-driven activity in column formation[147].

Topographic map formation

A topographic map results from the ordered projection of axons from an input structure, such as the retina, to higher target structures, such as the tectum or superior colliculus, so that adjacent cells in the input structure

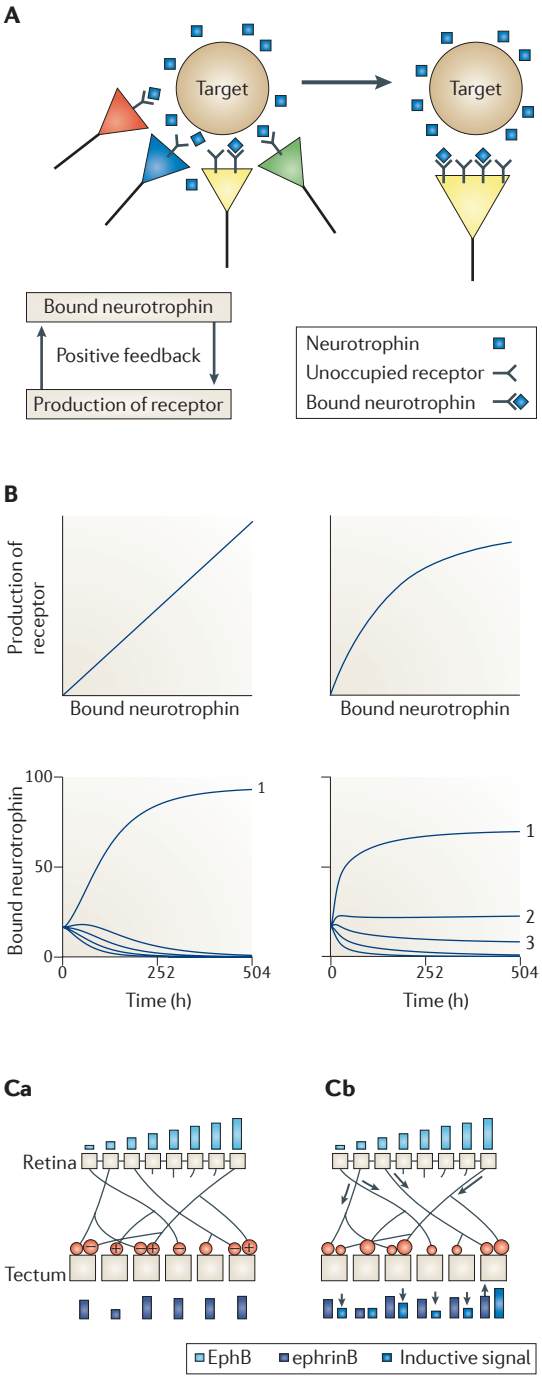

Figure 7 | **Modelling synaptic competition and topographic map formation. A** | Principles incorporated into a model of neurotrophin-mediated reduction of axonal innervation[123]. In this model, neurotrophin, which is needed for axon survival, is released by the target into the extracellular space and is bound to receptors at the axon. Binding of neurotrophin to receptors on the axon upregulates the production of neurotrophin receptors, as recently observed experimentally for nerve growth factor (NGF) and its receptor[124]. The more receptors an axon has, the more neurotrophin it can bind, which further increases the axon's number of receptors so that it can bind even more neurotrophin — at the expense of other axons. This positive feedback amplifies small differences in receptor number that might occur because of factors such as differences in presynaptic activity. **B** | This model has revealed how the upregulation function (which determines how the rate of receptor production varies with bound neurotrophin) might influence the pattern of innervation. The upper two graphs show upregulation functions and the lower two graphs show how the axons' amount of bound neurotrophin changes over time (if there is no bound neurotrophin, the axon has disappeared). Assuming that five axons are present initially, a linear upregulation function (upper left panel) results in a single innervating axon surviving (lower left panel). With a bounded function (upper right panel), multiple innervation develops (lower right panel). **C** | By two joint processes — synaptic strength modification and marker induction — a model showed how a retinal EphB gradient can be translated into a tectal ephrinB gradient, thereby creating a topographic mapping between retina and tectum[161]. The EphB densities are fixed, whereas the ephrinB densities can change. **Ca** | Each synaptic strength (shown by the size of the synaptic circle) is continually increased (shown by the + symbol) or decreased (shown by the – symbol) according to how closely the EphB density in the retinal cell resembles the ephrinB density in the tectal cell. **Cb** | Each ephrinB density is continually changed (shown by arrows below the tectal cells) to reduce the difference between the current ephrinB density and an inductive signal at each tectal cell. The inductive signal, coming from the retinal cells (shown by arrows along the axons), is made up of contributions from the axons innervating the cell. Each contribution is proportional to the strength of the synapse and the EphB density in the parent retinal cell. In this way, the EphB gradient is translated into an ephrinB gradient, whereby retinal cells with high EphB come to project to tectal cells with high ephrinB. In the EphA–ephrinA system, with slightly different rules, retinal cells with high EphA come to project to tectal cells with low ephrinA. Part **B** is reproduced, with permission, from REF 123 © (1999) The Royal Society. Part **C** is reproduced, with permission, from REF 161 © (2006) The Company of Biologists.

project to adjacent cells in the output structure[148]. The precise mechanisms by which such maps are formed during development are unknown, but they include molecular recognition, correlated electrical activity, neurotrophic factors, and outgrowth and retraction of axons and synapses. Computational models have investigated the contribution of these mechanisms to topographic map formation[132,148,149]. Although many models show map formation under normal circumstances, the challenge is to account for the various experimental results from surgical and genetic manipulations[150–152].

Activity-independent models of map formation. According to Sperry's chemoaffinity hypothesis[153] — initially formulated for the retinotectal system — each retinal ganglion cell carries information about its position within the retina in the form of a molecular label, and the axon of each retinal ganglion cell makes a connection with the cell in the target structure (tectum or superior colliculus) cell carrying the matching label.

A number of models[154–157] — based on this hypothesis and on the later discovered evidence for such labels in the form of gradients of Eph receptors in the retina and their ligands, the ephrins, in the target structure[158] — made these qualitative ideas more precise and have shown that mechanisms that use fixed labels can produce ordered maps, but are likely to be too rigid to account for the full map plasticity that has been observed[149,157].

In the marker induction model[159,160], the retinal labels are fixed, whereas the labels of the target cells can change. The retinal cells continuously transfer their labels onto the (initially unlabelled) target cells. A recent version of this model[161] explains the range of abnormal maps that were formed in EphA knock-in and knockout mice[151] (FIG. 7C). The model predicts what corresponding changes in ephrinA distribution in the colliculus should be found to be associated with the abnormal maps. The specific mechanism incorporated in the model, namely that labels in the target cells can be regulated by retinal labels, is amenable to experimental testing.

Activity-dependent models of map formation. In activity-dependent models of map formation, neighbourhood information in the retina is not encoded by molecular labels but by correlations in neural activity. Both in the retina and in the target structure, cells that are closer together are more likely to be active concurrently than cells that are farther apart, owing to lateral connections or the statistics of sensory input. Models have shown that if synaptic connections are strengthened in a Hebbian fashion, topographic maps emerge, as connections from retinal neighbours to neighbours in the target structure will be strengthened preferentially[162]. Models incorporating more complex rules for modifying synaptic strengths, such as STDP, also produce topographic maps[140,142].

As activity-independent mechanisms based on molecular markers are already sufficient for map formation, what is the role of activity? One common view is that activity refines a map that is already formed by other mechanisms. Because no single mechanism can probably explain all the data concerning map formation, an important role for modelling would be to help to tease out the contributions of the different mechanisms involved.

Recently, a multi-component model of map formation was developed[163] to study the interactions between molecular guidance cues, trophic factor release, spontaneous neural activity, STDP, synapse formation and deletion, and axon growth, branching and retraction. Although results from complex models are usually difficult to interpret, the authors found that instructive cues for axonal growth and map formation seem to be mediated first by molecular guidance and then by neural activity. As connection patterns ultimately result from axon growth and branching, models should frame map formation in terms of these processes because the physical and geometrical aspects of the axon place constraints on the development of connections[163,164].

Perspectives

Modelling studies in neuroscience are mostly concerned with the functioning of the mature brain. However, models are equally indispensable in achieving a true understanding of neural development.

The principles that enable neurons and networks to construct themselves will not be revealed by just identifying all of the genes and proteins involved. Even if all of the components and interactions are completely known, their collective behaviour is often difficult to deduce. Even a set of simple interactions can produce rich and unexpected dynamics. Models allow us to explore how high-level phenomena and dynamics (for example, neural tube formation) arise from the multitude of lower-level processes and interactions (for example, intercellular signalling, mechanical interactions, cell division, motion and adhesion).

In general, the most useful models are those in which the variables and parameters have a clear interpretation in the underlying biology, which enables comparison with experimental findings and experimental testing of model predictions. Many models outlined in this Review aim to account for, or 'postdict'[165], existing phenomena or data[18,23,43,143,161]. Several of the models have also made clear predictions, which were confirmed in the same study[51,84], confirmed in a later study[123], or are still awaiting experimental testing. Both predictions and 'postdictions' are valuable in advancing our understanding of neural development[165].

A challenge for future modelling studies of the early developmental stages (neural tube formation, cell migration and differentiation) is to further integrate mechanical processes (such as motion, adhesion and changes in cell shape) with intracellular genetic and protein networks. Changes in the cells' local extracellular environment as cells migrate create new input to the genetic networks that regulate cell motion and migration. Models provide the unique opportunity to explore the pattern generating potential of these complex reciprocal interactions.

In neuronal morphogenesis, axon–dendrite differentiation has been little explored but is a fruitful area for modelling, and models can help to unravel whether some

of the identified cellular and molecular mechanisms can provide feedback loops that are necessary for the establishment of neuronal polarity. A mechanistic insight into how the characteristic branching patterns of axons and dendrites arise from the concerted actions of intracellular pathways, extracellular signals and electrical activity is also still in its infancy. A useful strategy would be to try and translate some of the successful phenomenological models[58,61] into more biophysically based, mechanistic models, to investigate how the modulation of elongation and branching found in phenomenological models can emerge naturally from local, underlying biological processes.

A challenge for models of the establishment of connectivity, such as ocular dominance and topographic map formation, is to help to elucidate the contribution and interaction of molecular cues, spontaneous activity and sensory-driven activity. These models may also be framed more in terms of axon and dendrite outgrowth, as neuronal morphology will place important geometrical constraints on synaptic connectivity. To what extent, for example, can neuronal morphology, combined with a simple synapse formation rule based on proximity of axons and dendrites, already account for specific connectivity patterns[166]? In general, very few development models[107] have incorporated connectivity changes at the level of formation or deletion of synapses and outgrowth or retraction of axons and dendrites.

Important determinants of synaptic connectivity, such as neurite outgrowth, synaptic strengths and intrinsic neuronal excitability, are modulated by electrical activity. This gives rise to complex reciprocal interactions, with connectivity influencing activity dynamics and activity in turn affecting connectivity. Changes in connectivity thereby often seem to act to keep the average electrical activity of the neuron at a particular level[98]. Models have only just begun to address how this striving of neurons for activity homeostasis could shape synaptic connectivity patterns[99,105,106,107] as well as the intrinsic properties of neurons[167,168]. Activity homeostasis could serve as a general organizing principle for network formation, which may self-adjust neurons and connectivity to achieve and maintain functional performance.

Experiments provide valuable knowledge about the individual components involved in neural development, but to reason rigorously how the multitude of interactions among these components can produce the immense complexity of the nervous system will remain a great challenge that continues to require the help of mathematical and computational models. These efforts will ultimately help reveal the algorithmic principles by which the nervous system constructs itself.

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FURTHER INFORMATION
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