The complexity of living: when biology meets theory

Conference on Systems Dynamics of Intracellular Communication

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The second installment of the EMBO Conference Series on Systems Dynamics of Intracellular Communication, Spatial 2009: Overcoming Distance in Signaling Networks, took place between 15 and 19 March 2009, at Maale Hachamisha, Jerusalem Hills, Israel, and was organized by M. Fainzilber, G. Schiavo and B. Kholodenko.

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See Glossary for abbreviations used in this article.

Introduction

Like the previous meeting in this series in 2007 (Bronfman & Kapon, 2007), Spatial 2009: Overcoming Distance in Signaling Networks focused on understanding how cells and organisms are able to integrate signals in space and time. This broad topic was addressed by a multidisciplinary line up of speakers from diverse fields including

cell biology, bioinformatics, systems biology, physics, mathematics and genetics. Together, the various sessions covered major questions about biological processes that ranged from neurite growth and degeneration, spacing and patterning, and polarity and chemotaxis, to oscillations and noise, motor-driven traffic, and shape and size.

Cellular movements and signal propagation

The intricate spatial organization of many signalling pathways and protein interaction networks in cells has been investigated by using high-resolution imaging, new experimental techniques and improved analytical methods. The resulting observations have led to new theoretical models and *in vitro* experiments that provide a greater understanding of the highly coordinated spatial and temporal patterns within cells and during cell migration. More specifically, they have emphasized the fact that the precise localization on the membrane of active forms of soluble proteins, or clusters of proteins, has a key role in driving the formation of localized dynamic structures and cellular responses.

E. Stelzer (Heidelberg, Germany) presented a useful technical advance for the field by describing a new method for imaging cells and organisms that uses light sheet-based fluorescence microscopy (LSFM; Keller *et al*, 2008). LSFM excites only fluorophores in the illuminated plane, thus avoiding photo-damage, which gives the technique a distinct advantage for the fast imaging of sensitive biological specimens, as well as for *in vivo* imaging over long periods of time.

J. Hancock (Houston, TX, USA) reported on the dimensional control of signal transduction by Ras, the various isoforms of which display different lipid anchors and localize to distinct cellular compartments. Using FRET-FLIM methods, Hancock's team found that N-Ras-GTP is localized within cholesterol-rich regions, whereas N-Ras-GDP remains outside. Conversely, H-Ras-GDP is found inside lipid rafts, whereas the GTP form occurs outside. These findings point to the spatial organization of Ras signalling; in particular, nanoclusters of Ras exist within membranes, functioning as the sites of Raf/MEK/ERK recruitment and activation. Hancock showed that the number of nanoclusters is linearly dependent on EGF concentration. He proposed that this combination of behaviours allows the plasma membrane to achieve high-fidelity signal transmission by operating as an analogue–digital–analogue signal converter.

K. Kruse (Saarbrücken, Germany) reported recent theoretical and experimental studies of the Min protein system in *Escherichia coli*.

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Fig 1 | Spatiotemporal oscillations of bacterial Min proteins on supported membranes. (A) Schematic picture of the reactions and interactions in the Min system included in the theoretical model, including the different membrane-bound and soluble forms of MinD and MinE complexes. It is not yet clear which one, if any, dominates and generates the observed patterns. (B) Min protein surface waves *in vitro*. Confocal images of self-organized spiral protein waves on a supported lipid membrane, formed by labelled MinE (Loose *et al*, 2008).

The spatiotemporal distribution of Min proteins within bacteria has an essential role in the correct spatial localization of the septum that divides the cell. Computational models of this system have suggested that waves arise from interactions between the membrane-bound and soluble forms of MinD and MinE when ATP is present (Fig 1A). Kruse's laboratory confirmed this hypothesis by conducting *in vitro* experiments using purified Min proteins, ATP and a supporting lipid bilayer, with which they observed both planar and spiral waves (Fig 1B). Observation of these Min waves both *in vitro* and *in vivo* demonstrates that physiologically important subcellular structures can result from the dynamic self-organization of only a few interacting proteins (Loose *et al*, 2008).

R. Firtel (La Jolla, CA, USA) discussed the role of Ras in regulating directional sensing and cell migration in *Dictyostelium*. Firtel found that Ras is present at the leading edge of migrating cells and acts downstream from heterotrimeric G proteins. When a dominant negative form of RasG was expressed in cells lacking the Ras GEF Aimless, *Dictyostelium* lost its ability to sense the chemoattractant used in the experiment. To study the regulation of directionality sensing, Firtel's team isolated the partners of Aimless, which are the upstream activators of RasC and TOR Complex 2 (TorC2). Disruption of Aimless led to the impairment of RasC and TorC2 activation, downstream activation of PKB and chemotaxis, suggesting that the Aimless complex is a key component in the regulation of chemoattractant-induced PKB signalling.

Cellular networks: information processing and rhythms

Unravelling the dynamics of interaction networks inside cells remains a difficult challenge. These networks include gene-regulatory networks, metabolic control systems and protein interaction networks. Recent advances in computational modelling, combined with new experimental data, have allowed major breakthroughs in this area. B. Kholodenko (Dublin, Ireland) presented experimental and computational approaches to show how a concordant interplay between the insulin and EGF signalling networks can potentiate mitogenic signalling. Computational modelling unveiled that insulin endows the mitogenic EGFR pathway with robustness to perturbations of critical network nodes. Kholodenko's results showed the feasibility of using

computational models to predict complex cellular responses and identify therapeutic targets. A new strategy of unravelling functional interactions in cellular signalling and gene networks was proposed by demonstrating how dynamic connections leading to a particular module can be retrieved from experimentally measured network responses to perturbations influencing other modules.

J. Tyson (Blacksburg, VA, USA) described the classification of different types of 'minimal' biochemical oscillators (Novak & Tyson, 2008) by outlining the four key ingredients that are required for oscillatory temporal behaviour: negative feedback; sufficient time delay in the feedback signal (caused by transcription-translation delays, transport between the nucleus and cytoplasm, or long series of reactions in the negative feedback loop); sufficient nonlinearity in the kinetic equations; and proper balancing of time scales of the biochemical reactions. As an example of an oscillatory gene-regulatory network, Tyson described the circadian rhythms that govern the expression of the *PER* gene in fruit flies.

P. Bastiaens (Dortmund, Germany) reported how intracellular signalling networks process extracellular information and, in doing so, determine cellular phenotype. By using a reverse engineering approach, his laboratory investigated whether specific logical topologies—patterns of connections—in reaction networks occur in signalling, and whether and how these are able to give rise to specific responses to input signals. By sampling the reaction states of proteins in response to protein activity perturbations, Bastiaens was able to generate reaction diffusion models *in silico* populated with experimentally obtained kinetic parameters, capturing the experimentally observed spatial distribution of activity patterns. In doing so, he showed how the localization of protein reactions is controlled by gradient-generating reaction-diffusion mechanisms. It remains to be seen whether this demonstration of the cellular topography of activities that transmit signals from receptors at the cell surface is a universal mechanism for constraining and/or propagating the activity of freely diffusible proteins in the cytoplasm.

Overcoming distance, time and death in neurons

Neurons are the most polarized cells in the body and are highly dependent on correct intracellular transport for their development and survival. How they transmit and integrate signals over distances of up to 1 m in a human, in the case of motor neurons, is still poorly understood. D. Ginty (Baltimore, MD, USA) gave a presentation focused on neuronal development and the role of retrograde signalling. So far, the study of NGF-dependent mechanisms has been problematic because sympathetic neurons that cannot reach their target and source of NGF undergo apoptosis. By crossing Bax knockout mice to NGF knockout mice, to create mice in which both apoptosis and NGF signalling are abolished, Ginty observed a lack of final innervation, although axonal growth still occurred. Similarly, the neurotrophin NT3 was shown to be essential for organ targeting of axons. As both NGF and NT3 can bind to the neurotrophin receptor TrkA, their effect on the axonal retrograde transport of TrkA was investigated. Although NGF led to retrograde signalling, NT3 could not support survival through retrograde traffic when applied to distal axons of neurons *in vitro*. This suggests that the intracellular dynamics and signalling of a receptor could be dependent on its ligand.

A. Yaron (Rehovot, Israel) reported on the regulation of axonal degeneration during development, in which neurons of axons that cannot reach their target, or that have been damaged, are eliminated

by apoptosis. Previous reports have suggested that the Wld^S protein (a fusion between Ube4b and Nmnat1) is able to prevent axonal degeneration induced by injury, but not from developmental pruning (Hoopfer *et al*, 2006). Indeed, NAD⁺, the product of Nmnat1, can prevent axon degeneration *in vitro*. Yaron demonstrated that the pro-apoptotic protein Bax is required for axonal destruction on NGF withdrawal, which is known to lead to neuronal death, and that NAD⁺ protects against axotomy but not trophic withdrawal. In addition, Yaron found that apoptotic factors are activated within degenerating axons by trophic deprivation but not by axotomy. Surprisingly, the co-inhibition of caspases and NAD⁺ was required to protect axons from degeneration by trophic deprivation, suggesting that both pathways act downstream from Bax.

N. Kam (Rehovot, Israel) presented a computational study of different mechanisms that might explain the ability of neurons to respond differently to injuries depending on their location (Kam *et al*, 2009). He proposed two mechanisms for this. The first is a two-signal model in which signals are emitted from the injury site: a fast signal, presumably carried by the axonal electric potential, and a slow signal that is carried back to the cell body by dynein. The time difference between the arrival of the two signals provides the cell with a measurement of distance to the injury. The second mechanism is a two-detector model that involves a single slow signal and two detectors, one more sensitive than the other. In this scenario, the time delay between the activation of the two detectors provides the distance measurement. As Kam noted, only the two-detector model would allow cells to have robust distance-dependent responses, with a distance sensitivity of ~10% of the total axon length. These theoretical results will surely motivate future experiments to pinpoint the biological components of the proposed detection system in living neurons, *in vitro* and *in vivo*.

D. Holcman (Rehovot, Israel) presented a biophysical model for studying vesicle transport and microtubule (MT) dynamics during neurite outgrowth. Holcman showed that neurite outgrowth results from the vesicular delivery of membranes at the leading edge. The balance between vesicle exocytosis and endocytosis leads to a steady-state neurite length, which could be modulated through external cues. He reported three regimes by which outgrowth occurs depending on the degree of neurite stabilization induced by the MTs: strong neurite–MT coupling results in stable growth; reduced levels of coupling lead to a stochastic oscillatory regime; and further decreased levels of coupling result in the neurite exhibiting periods of collapse. The first and the third regimes characterize axonal and dendritic growth, respectively.

Several talks investigated the role of the endocytic pathway in axonal transport and neurotrophin-dependent signalling in neurons. S. Salinas (Montpellier, France) reported that CAV-2 is transported in a retrograde manner *in vivo* and transduces neurons that project towards the injection site. She analysed the dynamics and directionality of CAV-2 in primary motor neurons, revealing that CAV-2 and CAR, its cellular attachment molecule, are associated with transporting Rab7+ endosomes, suggesting that the virus takes advantage of the endogenous transport pathway of CAR. F. Bronfman (Santiago, Chile) discussed the role of Rab11 in BDNF-induced dendritic arborization in hippocampal neurons. She reported that BDNF induces dendritic ramification, and that the effect is increased by the activation of Rab11 and abolished by its inhibition. R. Kuruville (Baltimore, MD, USA) presented research on the regulation of anterograde transport of neurotrophin receptors during development. By using compartmentalized chambers

Glossary

Arp2/3	actin-related protein2/3 complex
BDNF	brain-derived neurotrophic factor
CAR	Coxsackievirus and adenovirus receptor
CAV-2	canine adenovirus type 2
Cdc42	cell division cycle 42
COXIV	cytochrome <i>c</i> oxidase IV
Crm1	chromosomal region maintenance 1
EGF	epidermal growth factor
EGFR	EGF receptor
ERK	extracellular signal regulated kinase
FISH	fluorescence <i>in situ</i> hybridization
FRET-FLIM	fluorescence resonance energy transfer-fluorescence lifetime imaging
GEF	guanine nucleotide exchange factor
GFP	green fluorescent protein
MAPK	mitogen-activated protein kinase
MEK	MAPK/ERK kinase
mRNA	messenger RNA
mRNP	messenger ribonucleoprotein
NAD ⁺	nicotinamide adenine dinucleotide
NGF	nerve growth factor
Nmnat1	nicotinamide mononucleotide adenylyl transferase 1
NT3	neurotrophin 3
PER	period
PKB	protein kinase B
RanBP1/2	RAN binding protein 1/2
RanGAP1	Ran GTPase activating protein 1
ROCK	Rho-associated coiled-coil forming protein
siRNA	small interfering RNA
TOR	target of rapamycin
Ube4b	ubiquitination factor E4B
UTR	untranslated region
Wld ^S	slow Wallerian degeneration protein

that allow the physical separation of neuronal cell bodies from nerve terminals, Kuruville's laboratory was able to observe the dynamics of TrkA endocytosis and transport in sympathetic neurons, leading her to propose that transcytosis is responsible for the axonal targeting of TrkA. Moreover, her observation that the internalization of TrkA is ligand-independent suggests that recycling could regulate the level of TrkA at the plasma membrane. Kuruville also showed that the inhibition of Rab11 leads to decreased axonal targeting of TrkA, whereas enhancing its activity increases the local response to NGF.

The studies reported here provide the experimental data and theoretical basis for a new understanding of the critical roles that active transport has in the formation and maintenance of axons and dendrites in nerve cells. Active transport across large distances and the complex spatial and temporal feedbacks that it creates will have to be integrated in future comprehensive models of these cells.

Intracellular transport, polarity and size

During embryonic growth, the establishment of polarity relies on the intracellular transport of signals and organelles to provide cues for cellular reorganization. S. Shvartsman (Princeton, NJ, USA) discussed the patterning signals that occur during *Drosophila* development. He found that some members of the MAPK pathway are present at either the embryo's anterior or posterior poles, where

Fig 2 | Localization of messenger RNAs coding for mitochondrial proteins to mitochondria. Endogenous *ATP2* messenger RNA ((mRNA) labelled with green fluorescent protein), which encodes a mitochondrial protein, is shown to be exclusively localized at the mitochondria (labelled with red fluorescent protein (RFP)) in yeast cells.

they help to establish a morphogen gradient. He was able to localize the mRNA encoding for Bicoid to the anterior pole, where it generates a local pool of the protein after translation. By contrast, MAPK itself was found to be activated at both the anterior and posterior ends. MAPK phosphorylates Bicoid by direct binding and this potentiates its activity. Shvartsman proposed that this binding has an antagonistic effect on MAPK phosphorylation and signalling, which results in the substrates competing for the kinase and creating a network that integrates the different patterning signals in a morphogenic gradient. N. Gov (Rehovot, Israel) presented a theoretical model whereby the transport and spatial localization of actin-regulating proteins along the length of the stereocilia determine the rate of actin polymerization and the overall distinct shape of these protrusions, which is essential for the formation of a functional auditory apparatus (Naoz *et al*, 2008).

L. Edelstein-Keshet (Vancouver, BC, Canada) reported that intracellular cycling between the cell membrane and the cytosol is essential for creating large diffusion gradients of the active and inactive forms of Rho. Edelstein-Keshet included several parameters in a two-dimensional simulation of a motile cell, including downstream signalling to Arp2/3-dependent actin filament branching, (un)capping actin barbed ends and actomyosin contraction. Including all these components in a model makes it more realistic, which makes it possible to reproduce the rich dynamics observed in motile cells; the model cell exhibited gradient-induced polarization, was able to change shape and motility, and was also able to reorient itself to new stimuli (Marée *et al*, 2006). Edelstein-Keshet's group showed that a phosphoinositide layer is not essential for basic motility and directionality, but that it mediates competition between conflicting 'frontness' zones in cases in which the cells encountered several stimuli or obstacles.

A. Ridley (London, UK) reported on the role of Rho GTPases in leukocyte polarity and migration. She found that, although the microtubule organizing centre (MTOC) is positioned by Cdc42 at the front

in migrating fibroblasts, in T cells, the MTOC and MTs are at the back. She demonstrated that the MT-destabilizing drug nocodazole induces a loss of T-cell polarity by activating RhoA, and that inhibiting the Rho effector ROCK restores the polarity of nocodazole-treated cells. She proposed that the Rho-ROCK pathway might help to reorganize MTs during leukocyte migration.

P. Lavia (Rome, Italy) discussed functional patterns of Ran and importin- β in human mitotic cells. It was previously proposed that the Ran network functions simply based on a gradient diffusion model, but Lavia showed that members of the network are in fact localized at specific mitotic structures, and that this localization has an important role. Lavia showed that RanBP1, Ran and importins accumulate at spindle poles and MTs. Ran and RanBP1 also comprise centrosomal fractions, whereas RanBP2, RanGAP1 and Crm1 localize to kinetochores. When Lavia destroyed the nucleation capacity of centrosomes, RanGTP relocalized from the poles to kinetochores, concomitant with the activation of MT nucleation from kinetochores. She also observed that during spindle formation, importin- β associates with MTs and dynein and regulates spindle organization and dynamics, and that MT-associated fractions of Ran and RanBP1 modulate these effects. Indeed, RanBP1 inactivation leads to MT hyperstabilization and apoptosis; this is markedly similar to the effects of taxol, a MT-stabilizing drug used in cancer treatment. Thus, the proteins that enable transport across the nuclear envelope are localized by specific MT-based structures, which therefore exert direct control over cell fate.

V. Allan (Manchester, UK) reported on the role of motor proteins in organelle transport. By using a GFP-ER marker, she showed that the ER moves bidirectionally along MTs and that inhibition of the dynein-regulator dynactin, by overexpressing p50 dynamitin, impairs the retrograde movement of the ER but not its anterograde transport. Interestingly, Allan showed that the morphology of the organelle changes from a tubular to a lamellar network under these circumstances. This suggests that both dynein and kinesin-1 have important roles in controlling ER dynamics and morphology.

From the experimental data and theoretical models presented at the meeting, it is apparent that the intracellular active transport of proteins and the localization of protein interactions drive the polarization of the cytoskeleton and the arrangement of the intracellular organelles, in both motile and stationary cells. The hope is that future models will incorporate more protein interaction networks to describe a larger variety of observed cellular behaviours, and that future experiments will put existing models to the test.

Creating localization: RNA transport in space and time

Another way in which cells achieve localized signalling is by synthesizing proteins directly at their site of action. The precise regulation of mRNA transport therefore provides localized signalling systems that can be modulated in time. J. Gerst (Rehovot, Israel) suggested that all mRNAs in eukaryotic cells might undergo intracellular transport to allow localized translation. He showed that, in general, mRNAs coding for mitochondrial proteins are targeted to mitochondria (Fig 2), that mRNAs encoding a subset of peroxisomal proteins are targeted to the peroxisome, that mRNAs encoding secreted and membrane proteins are targeted to the ER, and that mRNAs encoding proteins involved in cell polarization localize to the bud site in yeast. In the last case, Gerst showed that mRNA targeting to the bud site enriched the polarity machinery at the site of secretion. He proposed that mRNAs are not distributed diffusely, but are actively targeted through

cis-acting sequence elements and *trans*-acting RNA-binding proteins. Y. Shav-Tal (Ramat-Gan, Israel) discussed the spatial distribution and dynamics of mRNA in living cells. His laboratory uses the MS2 bacteriophage system, which allows the visualization of single mRNA molecules by fluorescent tagging and live-cell imaging. Using this technology, Shav-Tal's team was able to record the transport of mRNAs during the nuclear phase of mRNA transport. In particular, they determined the kinetics of transport and export of different mRNPs, and found that transport was not directed for all mRNPs examined but occurred by diffusion.

H. Krause (Toronto, ON, Canada) presented his studies of RNA localization in fly embryos. By using FISH probes, he showed that RNAs are localized in many unique ways, such as differentiated apical or basal expression, with many variants in between. Some RNAs also exhibit membrane-type localization and cell-cycle-based patterns, many of which overlap the localization patterns of their encoded proteins, suggesting a close relationship between protein and RNA localization. Of the approximately 4,000 genes that Krause screened, more than 70% of the RNAs were found to be localized in a subcellular manner. Interestingly, the localization of some nuclear RNAs was dependent on the siRNA pathway and the retention of mRNA in the nucleus.

In this vein, the translation of mRNAs in axons provides an efficient way for neurons to modulate local protein concentrations. J. Twiss (Wilmington, DE, USA) presented results on the spatial organization of mRNAs in neurons. He showed that β -actin mRNA accumulates in axons at the site of NGF stimulation and is involved in the local neurotrophin response (Willis *et al*, 2007), and that the 3' UTR of the calreticulin mRNA is responsible for its subcellular localization. In a similar way, the 3' UTR of GAP-43 drives the axonal targeting, and the localization element has been narrowed down to a region including the HuD binding site. B. Kaplan (Bethesda, MD, USA) reported results on the regulation of axonal mRNAs and mitochondrial activity by microRNAs. His laboratory isolated mRNAs encoding mitochondrial proteins including COXIV from axonal preparations; a sequence analysis of the 3' UTR of COXIV identified a target sequence for the microRNA miR-338. Kaplan showed that transfecting axons with the precursor of miR-338 decreases the levels of COXIV mRNA and protein and leads to a decrease in local mitochondrial activity. Conversely, anti-miR-338 oligonucleotides increase levels of COXIV, ATP generation and norepinephrine uptake. These mechanisms were shown to be strictly dependent on COXIV, because siRNA knockdown of COXIV led to their inhibition. Finally, it seems that miR-338 regulates axonal growth as pre-miR-338 transfection inhibits this process.

In summary, clear evidence was provided at Spatial 2009 that mRNA and protein production are highly localized in both space and time, so that proteins can be synthesized and used with maximal efficiency. Patterns of localization are found to have important roles within large cells, such as the axons of neurons, and in small cells such as yeast.

Conclusion

The overall complexity of living cells and organisms is being addressed both experimentally and computationally, as could be seen by the diverse range of work presented at this meeting. Within

cells, the spatial and temporal organization of chemical reactions and the assembly of multimolecular structures are orchestrated by numerous networks of interactions and fluxes. This organization is now found to be controlled by active transport processes based on molecular motors, and through the interplay between soluble and membrane-bound protein complexes. The cell is far from a uniform medium governed by diffusion alone, and active fluxes of chemical and vesicles, together with spatial localization and complex interaction networks, drive the formation of non-equilibrium patterns. From the axon of the neuron to the morphogenesis of the embryo, new experimental tools provide data with higher spatial and temporal resolution, allowing the development of more detailed theoretical models and computations. Where the quantitative models and experimental data converge, further understanding of the phenomena is achieved, and new principles governing cellular processes are being discovered. We look forward to the next meeting in this series, Spatial 2011, which will be co-organized by P. Bastiaens, J. Stelling and J. Twiss.

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