Gates for Conversation in Microbes

Subhoshmita Mondal[1*], Sarangam Majumdar[2]

ABSTRACT

Gate keeping has been useful to filter information for dispersal, whether for publication or some mode of communication. The ion channels in various microbes organize the flow of communication. The study of ion channels in bacteria has provided beginner insight to the neuron signalling, though the native role of ion channels in bacteria is yet indefinable. We have tried to summarize the structures of cell membranes bound with ion channels in prokaryotes and few eukaryotes. The signalling was combinedly proposed with information processing.

Key Words: Ion Channels, Prokaryotes, Eukaryotes, Information Processing

DOI Number: 10.14704/nq.2018.16.8.1128 **NeuroQuantology 2018; 16(8):1-8**

Introduction

The question arises why study ion channels in Microbes? They are the most amazing creatures endowed as model organism and are much more diverse than plants and animals. The researchers are trying to study and investigate in various ways and through numerous experiments about the structure and function of ion channels in microbes. The experimental advantages for selecting microbes are, specifically suited for genetic manipulation with very short replication times, simple to grow in large-scale laboratory culture conditions prerequisite for production of ion channel proteins for structural studies by X-ray crystallography or magnetic resonance spectroscopy, also, easily serves a large dense population to study the ion-gated signalling (Boris *et al*., 2008). The focus on microbes highlighted the 2003 Nobel Prize in Chemistry on structural and mechanistic studies of ion channels, which included bacterial ion channels (Mackinnon, 2003). Therefore, since the past years' microbes have advanced our understanding of biochemical and physiological cellular communications.

Communication has been always prevalent in biological systems. It exhibited signalling within organized densely packed cell commodities (Costerton *et al*., 1999; Hall-Stoodley *et al*., 2004; Vlamakis *et al*., 2008). The paper sum up the principles underlying structural and functional characterization of ion channels in prokaryotic (bacteria and archaea) and eukaryotic microbes (algae, ciliates and fungi). However, bacteria contributed mechanosensitive channels (Sukharev *et al*., 2004; Ian *et al*., 2007), K^+ channels (Perozo *et al*., 1999; Perozo *et al*., 1998; Schrempf *et al*., 1995), Na^+ channels (Pavlov *et al*., 2005; Ren *et al*., 2001), Cl^- channels (Dutzler *et al*., 2002), cNMP-gated channels (Clayton *et al*., 2004) and glutamate receptor channels (Chen *et al*., 1999) which enhanced our understanding of function of ion channels in living cells. Subsequently, the paper explains the concept of communication in two halves, the structure and function of ion gates and mathematical models to support the signalling through gates. It was studied to uncover, how microscopic bacteria can communicate effectively over large distances, mathematical models on propagations.

Corresponding author: Subhoshmita Mondal
Address: [1]Department of Chemical Engineering, Jadavpur University, Kolkata 700032, India; [2]Dipartimento di Ingegneria Scienze Informatiche e Matematica, Università degli Studi di L' Aquila, Via Vetoio – Loc. Coppito, 67010 L' Aquila – Italia
e-mail ✉ subhoshmita@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Received: 19 September 2017; **Accepted:** 24 July 2018

Scope of the Microbes

Mainly in human, the mouse, and the fly ion channels on the molecular levels were taken into account. Two developments explained the perception of ion channels in all three domains of life. First, patch-clamp assessment of the model microorganism *E. coli* (prokaryote) (Martinac *et al*., 1987) and eukaryotic *S.Cerevisiae* (Gustin *et al*., 1986) showed ion conductance of cell membranes. Second, the gradual increases in microbial genome sequences exposed gene products to be analogous to animal channels (Doyle *et al*., 1998). Accordingly, there is no specific method that can be applied to all microbes to study patch-clamping of membranes. Every type of microbial cell has to be deal individually. The "gating principle" in channel biology rarely experiences its open state without a stimulus.

It was reported, with the development of giant spheroplast in *Escherichia coli*, patch-clamp method was studied (Martinac *et al*., 1987; Ruthe *et al*., 1985). Briefly, *E. coli* cells subjected to culture condition of media contained antibiotic cephalexin. It was observed under microscope that the bacterial chains formed like strings of appropriate length. Apparently, EDTA and lysozyme was added to perforate the outer membrane with the breakage of glycosidic linkages that molded the string-like bacterial chain into spheroplasts (5–10 μm diameters). For further studies of MmaK (cyclic nucleotide-gated K+ channel) theses giant spheroplast preparation has been also optimized (Kuo *et al*., 2007).

Mechano-sensitive Channels in Microbes

The discovery of patch –clamp method in *E. coli* through the prepation of "giant spheroplast" explained well the structural and functional system of mechanosensitive (MS) class of membrane proteins in prokaryotes (Martinac *et al*., 1987; Ruthe and Adler, 1985). Although they selectively conduct ion, they referred as MS channels rather than MS ionic channels. The reason behind this is generally prokaryotes assist transport cellular osmoprotectants other than ions to regulate cellular turgor with osmosensors (Deininger *et al*., 1995). Bacterial MscL (Mechanosensitive channel of large conductance) possess conductance of ~3nS but lack ion specificity to whatsoever smaller than ~1,000 of molecular weight (including proline, potassium glutamate, trehalose, and ATP) (Kloda *et al*., 2008). The experiment that involved the cloning of MscL, contained fractionation of *E. coli* membrane by column chromatography and the patch-clamp examination of the individual protein fractions that re-formed into artificial liposomes (Sukharev *et al*., 1994). The isolated MscL protein comprised of 136 amino acid residues surveyed by cloning of its parallel *mscL* gene. The expression of the gene *in vivo* as well as *in vitro* of transcription or translation system confirmed that the *mscL* gene alone was responsible for the MscL activity (Sukharev *et al*., 1994). The structural investigation of MscL aimed many computer simulation studies to clear out the gate mechanism of channel with changes in membrane tension or composition. Stimulation examined the conformational modification of MscL protein structure by external force embedded in the lipid bilayer (Sukharev *et al*., 1993).

MscS studied in prokaryotes has a conductance of ~1nS and exhibits a slight fondness for anions over cations with a permeability ratio of Cl^- : K^+ = 1: 1.5-3.0. MscS and MscK were cloned to study after several years of the study of MscL (Levina *et al*., 1999). Two corresponding genes to MscS and MscK, *yggB* and *kefA* respectively were identified on chromosome of *E. coli.* The mechanosensitive channel of small conductance confirmed the deletion of the genes extinguished mechanosensitive currents. Nevertheless, at the same time, the activity of MscL remains intact in *E. coli* giant spheroplasts. However, MscS functionally differed from MscK by exhibiting fast inactivation on constant application of pressure (Koprowski and Kubalski, 2002). On the other hand, MscK showed sensitivity towards extracellular ionic environment (Li *et al*., 2002). The structural preview of MscS showed small membrane protein consist of 286 amino acids, whereas MscK is multidomain membrane protein comprised of 1120 amino acid residues. In their computational studies, most of the attempts by researchers drew attention to know more about the structure of channel and conduction state of the crystallized structure (Bass *et al*., 2002).

In case of eukaryotic mechanosensitive Ca^+ and K^+ channels are localized on the cell. It was studied when cilia in *Paramecium* was removed with ethanol (Jennings, 1906; Eckert, 1972). The deciliated cells that were mechanically stimulated showed that deciliated cells retained the depolarizing and hyperpolarizing mechanoreceptor responses, which specified the mechanosensitivity. *Paramecium* cells reversed their beat direction of cilia when observed under a low power microscope; many stimuli were assumed to be induced (Ogura and Machemer,

1980). Moreover, ciliated and deciliated cells showed decrease in depolarizing mechanosensitivity and a subsequent increase in hyperpolarizing mechanosensitivity, the moment when stimulation shifted the sites from the anterior to the posterior end of the cell. The structural study described that *Paramecium* cell causes Ca^{2+} based receptor potential with mechanical impact at the anterior end (Machemer and Ogura, 1979). Also, other divalent cations carried membrane depolarizing current (Ogura and Machemer, 1980), which could be the cause for backward ciliary movements. On the other hand, mechanical impact at the posterior end of the cell possessed a K^+-based hyperpolarization enhancing the cell to move forward due to an increase in frequency of the ciliary beat in normal direction (Eckert, 1972).

Gates of Ion-specific Channels in microbial Prokaryotes

Unlike the above-mentioned mechanosensitive channels, studies of prokaryotic ion-specific channels are not well organized. The recent decade investigated on atomic resolutions of prokaryotic K+ channels, Na+ channels and glutamate receptors (Boris *et al*., 2008). These structures served records of the molecular mechanisms of ion channels and reformed the research on field of ion-channel. These also provided vision to the understanding of ion-channels in bio-medical extensions. There are loads to study to uncover the roles they play in the various prokaryotic species.

In cytoplasm, K^+ is the foremost cation and their channel genes are found in almost genomes. The study of ion channels is engraved in neurophysiology with excitation of nerves or muscles involves the successive rise and fall of Na^+ and K^+ permeability of the membrane (Kuo, *et al*., 2005; Kuo *et al*., 2005). The functional feature describes, permeation to specific ion infers selectivity that acts like filter; rise and fall infers gateway control. K^+ channel has a property, that it can pass some 107 K^+ ions per second and differentiate against the smaller Na^+ at the same time; with a ratio greater than, K^+ : Na^+> 1,000 : 1(Boris *et al*., 2008). These properties challenge the concept of binding energy and binding specificity explained by the structural study of K^+-channel, KcsA of the bacterial. The question arises with puzzling feature on the control of filter and the gate in different channels. Superficially, the channels are stimulated with ligands, second messengers, voltage, heat, and mechanical force. The first KcsA structure was solved of *Streptomyces lividans* (Doyle *et al*., 1998). The K^+ filter of KcsA states that the channel resembles an inverted cone, with the gate closing towards the cytoplasmic end, and the filter located at the other end. The spatial geometry of sites on the filter does not coordinates and fit other cations such as Na^+ or Ca^{2+}. The ion filter is located near the outer surface of the membrane and held by bonds between the amino-acid residues in the filter sequence (TVGYG) (Chen *et al*., 1999). The structural conformations of filter which acts as a fixture is determined by the number and nature of the ions taken up (Domene and Sansom, 2003) as well as the bonds between constituent amino-acid residues. Generally, KcsA inactivation followed by activation where there is loss of channel current during inactivation with low K^+ concentration. In addition, the cNMP gated K^+ channels are trailed by sequences of cyclic nucleotide-binding domain (CNBD). MmaK protein expressed in *E.coli* supports the mode of gate opening by cyclic nucleotide (cNMP) (Gouaux and Mackinnon, 2005; Noskov and Roux, 2006). An unforeseen finding emerged from large-scale genome analyses is that prokaryotes express ion channels fit to molecular families long studied in neurons. It was studied that *Escherichia coli* uses chloride channels of the ClC family in the extreme acid resistance response with the ClC-ec1 protein. It stimulates H+ projection, activated during the extreme acid-resistance response common to enteric bacteria. The researchers have proposed that the channels work as an electrical shunt for an externally directed virtual proton pump linked to amino acid decarboxylation (Dutzler *et al*., 2002; Iyer *et al*., 2002; Nguitragool and Miller, 2006). The ionotropic glutamate receptors, bind glutamate or related neurotransmitters to open a cation conductance in excitatory postsynaptic membranes (Kuner *et al*., 2003). GluR0 protein is a prokaryotic homologue of mammalian glutamate receptors that forms glutamate-activated, potassium-selective ion channels (Arinaminpathy *et al*., 2003). Adherent communities of *Bacillus subtilis* forms biofilms and grow in interval of cycles once the colony reaches threshold size of population. It was seen by the authors; these oscillations arise when the cells present in the biofilms rundown of glutamate due to consumption of high amount of amino acid by peripheral cells. Glutamate starvation in the interior cells reduces the production of ammonium ions, which is required by the peripheral cells, thus

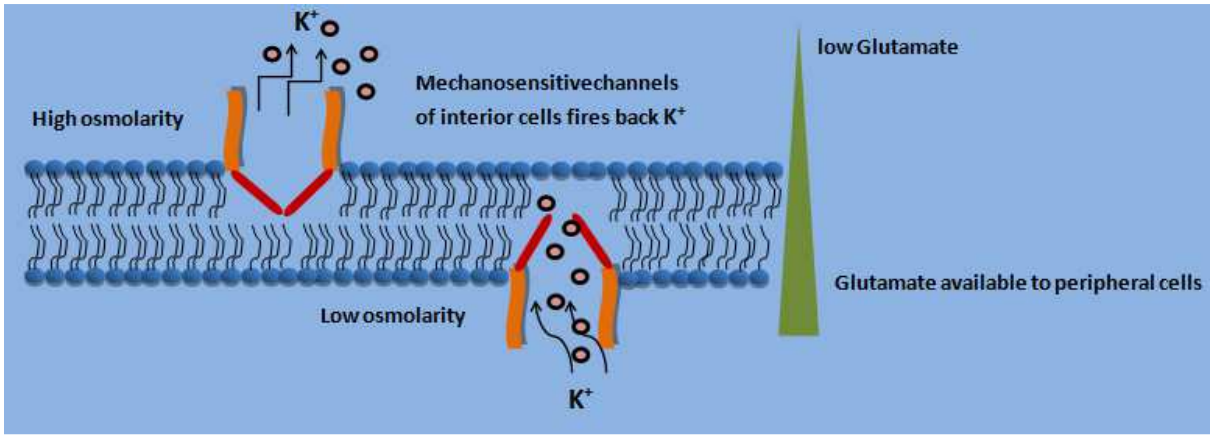

Figure 1. Gate-system in bacteria

the cell growth comes under arrest (Tolner *et al*., 1995; Sarah *et al*., 2015). Mathematical models on signaling solved to an extent, the question raised on how following linked metabolic processes of cells within the biofilm community travel a long distance of communication.

Gates of Ion-specific Channels in microbial Eukaryotes

The researches focused on nervous systems of vertebrates and larger invertebrates and studied the system of ion channel in eukaryotes. The functions of a number of ion channels in ciliates are well understood but the roles of most ion channels in eukaryotic microbes still to be explained. Fungi and protozoa are highly diverse and share a great deal of learning ion channels in these microorganisms. However, the gate in yeast is illustrated with the total K+ electrochemical gradient instead of voltage and this gate has been methodically dissected by genetically and biophysically (Loukin and Saimi , 2002).

In ciliates of *Paramecium* and *Stylonychia*, ion channels generate receptor potentials and action potentials. The sensitivity and transduction of external stimuli in these microorganisms occur at the unicellular level. The ion channels play a crucial in modulating the behavior of these ciliates by generating electrical membrane activity for signal integration and ion fluxes across their cell membranes comes under control. (de Peyer and Machemer , 1977; Deitmer, 1984; Kubalski *et al*., 1989; Machemer, 1988).

Paramecium was the first microbial cell investigated with two penetrated microelectrode intracellular recording (Kamada, 1934). Voltage-clamp experiments bared out membrane depolarization trigger Ca^{2+} dependent action potential with increase in intra-cilliary calcium concentration reversed the direction of *Paramecium* cell to beat backward. Meanwhile, with membrane hyperpolarization that trigger other ion currents leads the cell to move forward, which is more rapid due to ciliary beat in a normal direction (i.e, escape response) (Naitoh and Eckert, 1969; Naitoh and Eckert, 1973; Ogura and Machemer, 1980; Saimi and Martinac, 1989). These experiments helped to explore the K^+, Ca^{2+} and Na^+ currents that comprise of various action potentials bump into in a *Paramecium* cell. In a similar way, ciliate *Stylonychia* was examined by the classical two-microelectrode current and voltage-clamp methods. Simultaneous recording of responses of compound cilia in *Stylonychia* using membrane voltage-clamp and high frequency showed that membranelles beat at high frequency, whereas the frontal and marginal cirri are quiescent at the membrane resting potential. In contrast, membrane hyperpolarizations and depolarizations specifically activate the cirri without changing membranellar frequency (Deitmer *et al*., 1984; Machemer and Deitmer, 1987). The knowledge of fungal channels inherited from the budding yeast, *Saccharomyces cerevisiae*. In 1986, Michael C. Gustin found voltage-dependent ion in the plasma membrane of the yeast *Saccharomyces cerevisiae*. Ion channel activities observed and recorded from spheroplasts or patches of plasma membrane with the patch-clamp technique (Gustin *et al*., 1986; Gustin *et al*., 1988). The most precise activities came from a set of potassium channels with the properties of activation by positive but not negative voltages, high selectivity for potassium over sodium ion.

Ion channel of Bacterial toxins

Bacterial toxins are widely distributed proteins induced unhindered flux of ions and molecules across membranes. They are frequently cytotoxic as they perforate the cell membranes by creating unregulated pores across the membrane of susceptible cells that causes cell death and lysis. Among the bacterial toxins the pore-forming colicins were first to be discovered in the process of searching for ways to kill bacteria (Gratia, 1925; Gilbert , 2002). Colicins produced by colicinogenic strains of non-pathogenic *Escherichia coli* and some related species of *Enterobacteriaceae*. Colicins primarily target membranes of susceptible bacterial strains to inhibit their growth and thus present a major weapon in the on-going bacterial warfare. They form voltage-dependent ion channels by interacting simultaneously with several components of the complex membrane of susceptible cells and transforming themselves into α-helical membrane-spanning channel proteins (Lakey *et al*., 2001). An interesting case on its own presents VacA, the pore-forming toxin of the stomach ulcer causing bacterium *Helicobacter pylori*. In contrast to most bacterial toxins, which usually form membrane pores without preference for permeating ions, VacA exhibits electrophysiological properties characteristic of the ClC channels of eukaryotic host cells (Czajkowsky *et al*., 2005). In addition to sharing similar conductance and ionic selectivity with the ClC channels VacA also shares an open probability dependent on the molar ratio of permeable ions as well as single channel events resolvable as two independent, voltage-dependent transitions, which are the very characteristic of the ClC channels. The only feature distinguishing VacA from the ClC channels is the membrane potential at which the two channels close. VacA toxin thus largely mimics the electrophysiological behavior of ClC channels of the host cells suggesting a novel mechanism of toxin action. (Boris *et al*., 2008)

Signal Integration Circuit and information processing

Current researches determined that the ion channels conduct long-range electrical signals within bacterial biofilm through spatially propagating waves of potassium. These waves possessed a positive feedback loop, in which a metabolic trigger induces release of intra cellular potassium, which in turn depolarizes the neighboring cells. Propagating through biofilm, this wave of depolarization coordinates metabolic states among cells in the interior as well as sideline of biofilm. Removal of the potassium channel abolishes the response of propagation was suggested (Prindle *et al*., 2015).

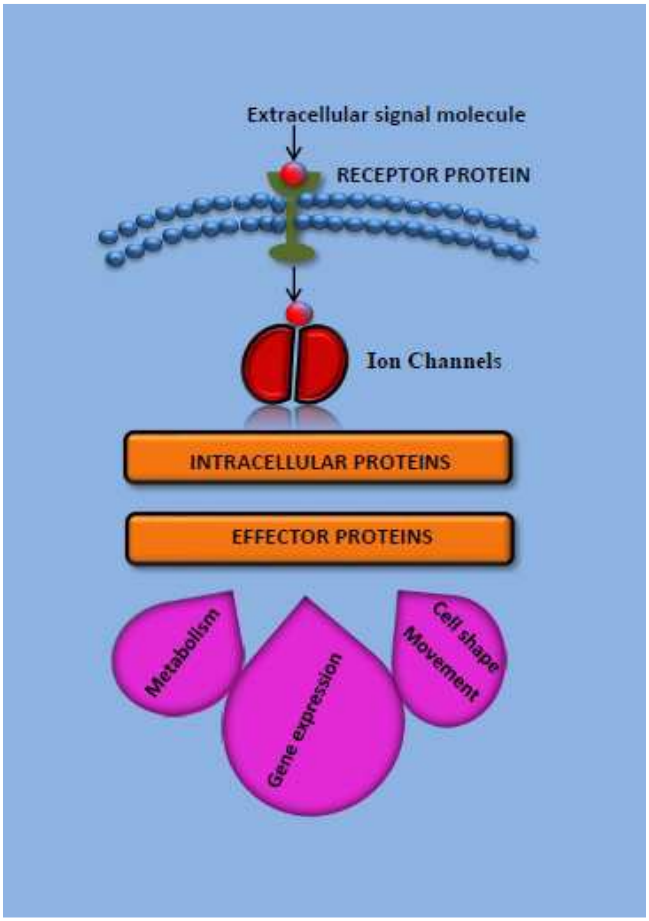

Figure 2. Route model of signaling

Moreover, it was studied spatial propagation can be hindered by specific genetic perturbations to potassium channel gating also. Altogether, these results demonstrated functional ion channels in bacterial biofilms, and provided a prokaryotic example for active, long-range electrical signaling in cellular communities (Prindle *et al*., 2015).

The quorum sensing signals integrated which form circuits and can learn about their environments using more than one autoinducers since all signaling pathways merge in one. For example, *Vibrio harveyi* produces three distinct autoinducers (AIs), the AI-1, produced only by *V. harveyi*, the CAI-1, which produced by *Vibrio* species and is probably used as intra genera signal and AI-2 produced by a large variety of bacteria and is probably useful for interspecies signal. The three autoinducers, AI-1, CAI-1, and AI-2 are detected by three different transmembrane two-

component receptors, LuxN, CqsS, and LuxPQ, respectively (Xavier and Bassler, 2003) (Henke and Bassler, 2004). In state of zero-input conditions, i.e., in the case where no AI's are detected, the receptors act as kinases that relay phosphate to the LuxU. Phosphorylated LuxU, LuxU-P, phosphorylates LuxO to LuxO-P, which in turn activates the transcription of genes encoding five small regulatory RNAs (sRNAs), called Qrr1-5. These sRNAs in conjunction with Hfq destabilize the mRNA that encodes the master quorum-sensing regulator LuxR. On the other hand, in state of non-zero input conditions, i.e., in the case where AI's were detected, the AIs convert the receptors to a phosphatase state and the phosphorylation process is reversed. As a result, LuxO-P is dephosphorylated and becomes inactive, the genes encoding the Qrr1-5 are not transcribed, the mRNA that encodes LuxR is translated and LuxR is produced (Long, 2009).

A quantum gate circuit model of signal integration (Karafyllidis, 2012) has been proposed which incorporates quantum information processing as a theoretical framework for the learning of signal processing in biological system. This model determined recent static experimental results precisely and the dynamic response of the quorum sensing circuit quite reasonably. A simulation algorithm based on this model has been developed and numerical experiments that evaluated the dynamical operation of the quorum sensing circuit in various cases of AI's.

In general, classical information processing use quantum channels. Biological information processing takes place at the challenging regime where quantum meets classical physics. The majority of information in a cell is classical information, which has the advantage of being reliable and easy to store. The quantum aspects enter when information is processed. Any interaction in a cell relies on chemical reactions dominated by quantum aspects of electron shells, i.e. quantum mechanics controls the flow of information. The combined classical-quantum aspects of information processing keep a track with this concept, formally known as a classical-quantum state in biological term. In more detail, information processing in DNA was studied. The impact of quantum noise on the classical information processing investigated the copying of genetic information. Quantum effects did not play vital role in large scale in field of biology. It is not only difficult to maintain coherence at body temperature in a noisy system, but living systems themselves have little use of phase information which is a crucial component of quantum computers. The functionality of cells or bacteria depends on a delicate balance of concentrations of different molecules. Therefore, the majority of information in a cell is classical information that has the advantage of being reliable and easy to store. The quantum aspects enter when information is processed. Any interaction in a cell relies on chemical reactions, dominated by quantum aspects of electron shells, i.e. quantum mechanics controls the flow of information. This insight is far from being new. The division of molecules into a classical part and a quantum part is a key aspect of the Born-Oppenheimer approximation used successfully for many problems in computational chemistry since 1927 (Elisabeth, 2011). The Born-Oppenheimer approximation starts with separating complex molecules into the set of coordinates of the heavy nuclei, treated as classical particles, and the light electrons, which are treated fully quantum mechanically. The set of nuclei determines via the Schrödinger equation the electronic state of the molecule. Any interaction in a cell uses chemical reactions, determined by the electronic states of the molecules. A chemical reaction can turn a given molecule into a different one, thus changing the classical information. This formalism is able to keep track of the combined classical-quantum aspects of information processing.

References

Arinaminpathy Y, Biggin PC, Shrivastava IH, Sansom MS. A prokaryotic glutamate receptor: homology modelling and molecular dynamics simulations of GluR0. FEBS Letters 2003; 553(3): 321-27.

Bass RB, Strop P, Barclay M, Rees DC. Crystal structure of Escherichia coli MscS, a voltage-modulated and mechanosensitive channel. Science 2002; 298(5598): 1582-87.

Beagle SD, Lockless SW. Microbiology: electrical signalling goes bacterial. Nature 2015; 527(7576): 44-45.

Booth IR, Edwards MD, Black S, Schumann U, Miller S. Mechanosensitive channels in bacteria: signs of closure?. Nature Reviews Microbiology 2007; 5(6):431-40.

Chen GQ, Cui C, Mayer ML, Gouaux E. Functional characterization of a potassium-selective prokaryotic glutamate receptor. Nature 1999; 402(6763): 817-21.

Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. Science 1999; 284(5418): 1318-22.

Czajkowsky DM, Iwamoto H, Szabo G, Cover TL, Shao Z. Mimicry of a host anion channel by a Helicobacter pylori pore-forming toxin. Biophysical Journal 2005; 89(5): 3093-101.

de Peyer JE, Machemer H. Membrane excitability inStylonychia: Properties of the two-peak regenerative Ca-

response. Journal of Comparative Physiology 1977; 121(1): 15-32.
Deininger W, Kröger P, Hegemann U, Lottspeich F, Hegemann P. Chlamyrhodopsin represents a new type of sensory photoreceptor. The EMBO Journal 1995;14(23): 5849-58.
Deitmer JW, Machemer H, Martinac B. Motor control in three types of ciliary organelles in the ciliateStylonychia. Journal of Comparative Physiology A 1984; 154(1): 113-20.
Deitmer JW. Evidence for two voltage-dependent calcium currents in the membrane of the ciliate Stylonychia. The Journal of Physiology 1984; 355(1): 137-59.
Domene C, Sansom MS. Potassium channel, ions, and water: simulation studies based on the high resolution X-ray structure of KcsA. Biophysical Journal 2003; 85(5): 2787-800.
Doyle DA, Cabral JM, Pfuetzner RA, Kuo A, Gulbis JM, Cohen SL, Chait BT, MacKinnon R. The structure of the potassium channel: molecular basis of K+ conduction and selectivity. Science 1998; 280(5360): 69-77.
Dutzler R, Campbell EB, Cadene M, Chait BT, MacKinnon R. X-ray structure of a ClC chloride channel at 3.0 Å reveals the molecular basis of anion selectivity. Nature 2002; 415(6869): 287-94.
Eckert R. Bioelectric control of ciliary activity. Science 1972; 176(4034): 473-81.
Gilbert RJ. Pore-forming toxins. Cellular and Molecular Life Sciences CMLS 2002; 59(5): 832-44.
Gouaux E, MacKinnon R. Principles of selective ion transport in channels and pumps. Science 2005; 310(5753): 1461-65.
Gratia A. Sur un remarquable exemple d'antagonisme entre deux souches de coilbacille. CR Seances Soc. Biol. Fil. 1925; 93: 1040-41.
Gustin MC, Martinac B, Saimi Y, Culbertson MR, Kung C. Ion channels in yeast. Science 1986; 233(4769): 1195-97.
Gustin MC, Zhou XL, Martinac B, Kung C. A mechanosensitive ion channel in the yeast plasma membrane. Science 1988; 242(4879): 762-65.
Hall-Stoodley L, Costerton JW, Stoodley P. Bacterial biofilms: from the natural environment to infectious diseases. Nature Reviews Microbiology 2004; 2(2): 95-108.
Henke JM, Bassler BL. Three parallel quorum-sensing systems regulate gene expression in Vibrio harveyi. Journal of Bacteriology 2004; 186(20): 6902-14.
Iyer R, Iverson TM, Accardi A, Miller C. A biological role for prokaryotic ClC chloride channels. Nature 2002; 419(6908):715–18.
Jennings HS. Behavior of lower organisms. Bloomington: Indiana University Press, 1906.
Kamada T. Some observations on potential differences across the ectoplasm membrane of Paramecium. Journal of Experimental Biology 1934; 11(1): 94-102.
Karafyllidis IG. Quantum gate circuit model of signal integration in bacterial quorum sensing. IEEE/ACM Transactions on Computational Biology and Bioinformatics (TCBB) 2012; 9(2):571-79.
Kloda A, Petrov E, Meyer GR, Nguyen T, Hurst AC, Hool L, Martinac B. Mechanosensitive channel of large conductance. The İnternational Journal of Biochemistry & Cell Biology 2008; 40(2): 164-69.
Koprowski P, Kubalski A. Voltage-independent adaptation of mechanosensitive channels in Escherichia coli protoplasts. The Journal of Membrane Biology 1998; 164(3): 253-62.
Kubalski A, Martinac B, Saimi Y. Proteolytic activation of a hyperpolarization-and calcium-dependent potassium channel inParamecium. The Journal of Membrane Biology 1989; 112(1): 91-96.
Kuner T, Seeburg PH, Guy HR. A common architecture for K+ channels and ionotropic glutamate receptors?. Trends in Neurosciences 2003; 26(1): 27-32.
Kuo MM, Haynes WJ, Loukin SH, Kung C, Saimi Y. Prokaryotic K+ channels: from crystal structures to diversity. FEMS microbiology Reviews 2005; 29(5): 961-85.
Kuo MM, Saimi Y, Kung C, Choe S. Patch clamp and phenotypic analyses of a prokaryotic cyclic nucleotide-gated K+ channel using Escherichia coli as a host. Journal of Biological Chemistry 2007; 282(33): 24294-301.
Kuo MM, Saimi Y, Kung C. K+ channels: a survey and a case study of Kch of Escherichia coli. InBacterial Ion Channels and Their Eukaryotic Homologs. Washington DC: American Society of Microbiology, 2005: 1-20.
Lakey JH, Slatin SL. Pore-forming colicins and their relatives. InPore-forming toxins. Berlin: Springer, 2001: 131-61.
Levina N, Tötemeyer S, Stokes NR, Louis P, Jones MA, Booth IR. Protection of Escherichia coli cells against extreme turgor by activation of MscS and MscL mechanosensitive channels: identification of genes required for MscS activity. The EMBO Journal 1999; 18(7): 1730-37.
Li Y, Moe PC, Chandrasekaran S, Booth IR, Blount P. Ionic regulation of MscK, a mechanosensitive channel from Escherichia coli. The EMBO Journal 2002; 21(20): 5323-30.
Long T, Tu KC, Wang Y, Mehta P, Ong NP, Bassler BL, Wingreen NS. Quantifying the integration of quorum-sensing signals with single-cell resolution. PLoS Biology 2009; 7(3): e1000068.
Loukin SH, Saimi Y. Carboxyl tail prevents yeast K+ channel closure: proposal of an integrated model of TOK1 gating. Biophysical Journal 2002; 82(2): 781-92.
Machemer H, Ogura A. Ionic conductances of membranes in ciliated and deciliated Paramecium. The Journal of Physiology 1979; 296(1): 49-60.
Machemer H. From structure to behaviour; Stylonychia as a model system for cellular physiology. Progr In Protistol. Bristol: Biopress Ltd, 1987; 2: 213-330.
Machemer H. Motor control of cilia. In: Goertz, HD., editor. Paramecium. Berlin: Springer Verlag, 1988: 216-35.
Mackinnon R. The Atomic Basis of Selective Ion Conduction in Potassium Channels. Nobel Lecture. http://nobelprize.org/chemistry/laureates/2003/mackinnon-lecture.html
Martinac B, Buechner M, Delcour AH, Adler J, Kung C. Pressure-sensitive ion channel in Escherichia coli. Proceedings of the National Academy of Sciences 1987; 84(8): 2297-301.
Martinac B, Saimi Y, Kung C. Ion channels in microbes. Physiological Reviews 2008; 88(4): 1449-90.
Naıtoh Y, Eckert R. Sensory mechanisms in Paramecium: II. ionic basis of the hyperpolarizing mechanoreceptor potential. Journal of Experimental Biology 1973; 59(1): 53-65.
Naitoh Y, Eckert R. Ionic mechanisms controlling behavioral responses of Paramecium to mechanical stimulation. Science 1969; 164(3882): 963-65.
Nguitragool W, Miller C. Uncoupling of a CLC Cl−/H+ exchange transporter by polyatomic anions. Journal of Molecular Biology 2006; 362(4): 682-90.
Noskov SY, Roux B. Ion selectivity in potassium channels. Biophysical Chemistry 2006; 124(3): 279-91.

Ogura A, Machemer H. Distribution of mechanoreceptor channels in theParamecium surface membrane. Journal of Comparative Physiology 1980; 135(3): 233-42.

Pavlov E, Bladen C, Diao C, French RJ. Bacterial Na channels: progenitors, progeny, or parallel evolution?. InBacterial Ion Channels and Their Eukaryotic Homologs. Washington, DC: American Society of Microbiology, 2005: 191-207.

Perozo E, Cortes DM, Cuello LG. Three-dimensional architecture and gating mechanism of a K+ channel studied by EPR spectroscopy. Nature Structural and Molecular Biology 1998; 5(6): 459–69.

Perozo E, Marien D, Cuello LG. Structural rearrangements underlying K+-channel activation gating. Science 1999; 285(5424): 73-78.

Prindle A, Liu J, Asally M, Ly S, Garcia-Ojalvo J, Süel GM. Ion channels enable electrical communication in bacterial communities. Nature 2015; 527(7576): 59-63.

Ren D, Navarro B, Xu H, Yue L, Shi Q, Clapham DE. A prokaryotic voltage-gated sodium channel. Science 2001; 294(5550): 2372-75.

Rieper E. Quantum Coherence in Biological Systems (Doctoral dissertation). Centre for Quantum Technologies, 2011.

Ruthe HJ, Adler J. Fusion of bacterial spheroplasts by electric fields. Biochimica et Biophysica Acta (BBA)-Biomembranes 1985; 819(1): 105-13.

Saimi Y, Martinac B. Calcium-dependent potassium channel inParamecium studied under patch clamp. The Journal of Membrane Biology 1989; 112(1): 79-89.

Schrempf H, Schmidt O, Kümmerlen R, Hinnah S, Müller D, Betzler M, Steinkamp T, Wagner R. A prokaryotic potassium ion channel with two predicted transmembrane segments from Streptomyces lividans. The EMBO Journal 1995; 14(21): 5170-78.

Sukharev SI, Blount P, Martinac B, Blattner FR, Kung C. A large-conductance mechanosensitive channel in E. coli encoded by mscL alone. Nature 1994; 368(6468): 265–68.

Sukharev SI, Martinac B, Arshavsky VY, Kung CH. Two types of mechanosensitive channels in the Escherichia coli cell envelope: solubilization and functional reconstitution. Biophysical Journal 1993; 65(1): 177-83.

Sukharev SI, Martinac B, Blount P, Kung C. Functional reconstitution as an assay for biochemical isolation of channel proteins: application to the molecular identification of a bacterial mechanosensitive channel. Methods 1994; 6(1): 51-59.

Tolner B, Ubbink-Kok T, Poolman B, Konings WN. Characterization of the proton/glutamate symport protein of Bacillus subtilis and its functional expression in Escherichia coli. Journal of Bacteriology 1995; 177(10): 2863-69.

Vlamakis H, Aguilar C, Losick R, Kolter R. Control of cell fate by the formation of an architecturally complex bacterial community. Genes & Development 2008; 22(7): 945-53.

Xavier KB, Bassler BL. LuxS quorum sensing: more than just a numbers game. Current Opinion in Microbiology 2003; 6(2): 191-97.

Yoshimura K, Nomura T, Sokabe M. Loss-of-function mutations at the rim of the funnel of mechanosensitive channel MscL. Biophysical journal 2004; 86(4): 2113-20.