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Cell Signalling and Pathways Explained in Relation to Music and Musicians

John T. Hancock
University of the West of England, Bristol, UK

1. Introduction

Cell signalling is arguably the most important area of modern biology. The subject encompasses the control of cellular events, especially in response to extracellular factors. It has been suggested that the human body is one of the most complex machines ever produced (Dawkins, 1989) and the regulation of the activities within it are also equally complex.

Interest in cell signalling does not simply stem from an academic viewpoint either. Certainly there is a vast resource of research which is focuses on the investigation of signalling pathways and the control which they bestow on a cell. However, there are tangible reasons to take an interest here too. The vast majority of new pharmaceutical compounds under development are aimed at the modulation of proteins involved in cell signalling events (Filmore, 2004). Such proteins may be G protein-coupled receptors (GPCRs) or perhaps kinases which are downstream of such receptors. Many anti-cancer studies are now focused on the development of compounds which modulate Mitogen Activated Protein Kinases (MAPKs) for example. Therefore, an understanding the working of the components of a signal transduction opens up avenues for the future modulation of such activities with the development of new therapies and pharmaceutical agents.

The study of cell signalling can seem very daunting. Vast diagrams full of acronyms can put off the most ardent reader, but there are many basic principles which underpin the subject. In cell signalling compounds are made and initiate a response, and this is true whether the molecule originates outside the cell or is created inside. The signal transduction pathway carries a "message", with such a message originating in one place, either outside of the cell, or from another part of the same cell, but having a response elsewhere. The keys to cell signalling are that the message needs to be conveyed in a specific manner, so that it is not scrambled and misconstrued and that the cell must be able in most cases to revert back to a state or activity in which it was engaged before the message arrived, that is, the signal transduction pathway needs to be stopped when the message is no longer needed to be conveyed.

Even though the principles are simple, it is still hard to understand the complexities of cell signalling. Often signalling events are over-simplified, and components are aligned in neat rows. However, a more holistic view shows that signalling is extremely complicated and hard to understand. There are many books and chapters which explain cell signalling (Hancock, 2003; Hancock, 2010; Krauss, 2008) but these are all based on the description of

the science, with the molecular details often putting off the reader who may be new to the field. Therefore, often an analogy to explain such a complex subject would be very useful, and may offer a more attractive way to teach the subject and to engage those who seek a better understanding of the area of study. In this chapter music is used as an analogy to try to shed light on some of the events in cell signalling. It has already been suggested that the use of such an analogy will be useful to those trying to get to grips with the subject (Hancock, 2005; 2009) and this chapter will expand and elaborate on those ideas. It is suggested that this can be used by those studying and teaching cell signalling.

2. Music and musical terminology

Listening to music and watching music being played are both events which rely on cell signalling. Sound waves are perceived in the ear, while photons are sensed in the eye and both lead to downstream series of signal transduction events (Hancock, 2010). In fact early work which led to the discovery of a major class of proteins, the G proteins, was due to work on the eye (Fung & Stryer, 1980). However, this is not of particular relevance to the discussion here. There is, however, growing, if controversial evidence that music can have effects on biological systems, including humans (Trappe, 2010). A term has been coined, "The Mozart Effect". This has come about from work where Mozart's music has been played and effects measured. Some tangible effects have been reported, perhaps more in the popular press than the scientific literature, but there are examples of serious reports looking into this (Jenkins, 2001).

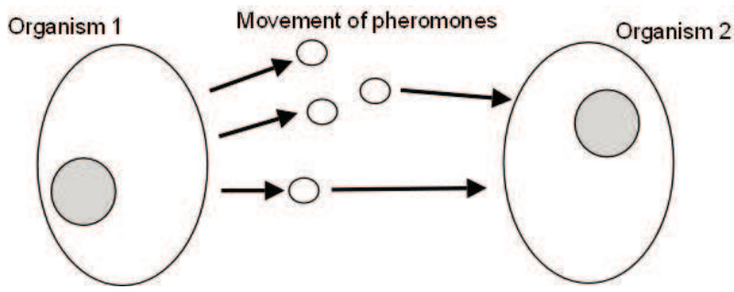


Fig. 1. Movement of pheromones transmits signals between individuals in a population. One organism releases a compound which is sensed by a second individual, in which a response is mounted. Pheromones could be thought of as music moving through the medium separating the two organisms.

Of course it is not only humans which are responsive to sound with studies reporting effects on plants for example (Qin *et al*., 2003). Mechanical action on cells has been shown to affect cellular function (Wan *et al*., 2004) and this includes exposure to music. For example, the activity or expression of some proteins has been shown to be changed if music is played (Chikahisa *et al*., 2006).

Not only does music provoke cell signalling events in organisms, but music terminology is often used to describe such cellular activities. It is often said in research papers that a signalling molecule "orchestrates" or "conducts" events for example (Polo & de Fiore, 2008). In his most recent book Nick Lane uses music to explain his thinking on more than one occasion. On the theme of biological variation he discusses the musical variations of Bach and Beethoven. On the topic of protein structure he says "Yet the deeper music of the protein spheres is still there to be discerned by crystallography" and later when talking

about the eye he writes "Like an orchestral conductor conjuring up the most beautiful music without sounding a note himself, the gene calls forth the structures of the eye by ushering in individual players, each with their own part to play" (Nick Lane, 2010). Therefore it is an extension of this idea which can enable music in its wider sense to act as an analogy for cell signalling. Previously the idea has been discussed (Hancock 2005; 2009) but here the ideas are expanded and enhanced.

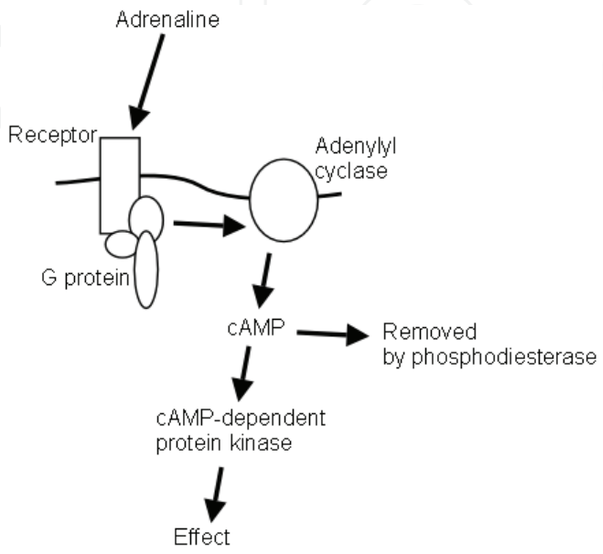


Fig. 2. cAMP is involved in the signalling invoked by adrenaline. Adrenaline is received by a plasma membrane bound receptor. The receptor is linked to a heterotrimeric G protein, which releases its alpha subunit on activation. The G protein subunit can activate adenylyl cyclase which resides in the plasma membrane. Adenylyl cyclase produces cAMP from ATP. cAMP can activate cAMP- dependent protein kinase and so lead to downstream responses. cAMP is removed by the action of phosphodiesterase.

3. Signals between organisms

Music is often produced by an individual or group of individuals, and listened to, or perceived by, another individual or group of individuals. There is an excellent example of such action in cell signalling and that is the generation and response to pheromones (Agosta, 1992; Kell *et al*., 1995). Here small compounds are made and released into the medium outside of the organism (Figure 1). They are then carried in the flow of the liquid or gas, perhaps the atmosphere, which surrounds the organism to be sensed and responded to by another individual of the same species, but not the individual organism that released them. Pheromones are used for attracting a mate and sexual arousal for example. In human behaviour interestingly often music is used for the same purpose.

4. Production of signals

For a cell to use a molecule in a cell signalling pathway it needs to firstly be made. Many of the components are constitutively produced and are present to partake in the required activity when called upon to do so. Examples would be large proteins such as kinases.

However, there are many situations where a molecule needs to be present, or released, in a rapid manner. Cyclic AMP (cAMP) for example is needed in response to adrenaline (for an example of a signalling pathway in which cAMP is involved see Figure 2) while insulin is released in to the blood stream when required. One of the main underlying principles of signalling is that the system is able to convey the message when and where required, in a temporal manner appropriate to the required response. Therefore molecules need to be able to partake in such signalling when called upon to do so.

There are two main ways to make a signal. Either the molecule is produced when required, or it is made and stored, to be released when required (Figure 3). It a similar manner it could be argued that there are two main ways to listen to music. You either go to a concert and in the presence of the musical instruments you listen to the sounds being made, or you let the band record the music, store it until required and then play it. In this scenario the instruments are the enzymes, producing the message. At the concert instruments make the signal as needed, to the required amount, for the required time. This is just like an enzyme such as adenylyl cyclase which is turned on, generates cyclic AMP (cAMP) for a set period of time, and then turns off. Just like the person at the concert, the protein responding to cAMP can perceive its presence and when it is all over revert back to a quiescent state – concert over.

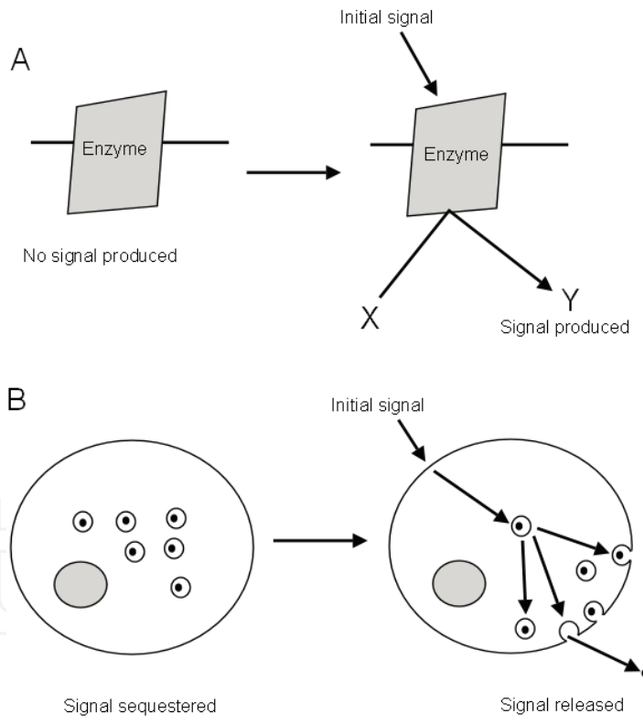


Fig. 3. Signals can be generated using different scenarios. In (A) there is no signal produced until an enzyme is activated. At that point a compound X and be converted to compound Y, so generating a signal. That is Y can now be recognised and a response or effect produced due to its presence. In (B) the signalling molecule can be pre-made but sequestered into vesicles. On arrival of the appropriate stimulus the vesicles will translocate to the plasma membrane for example. The signalling molecule will then be released and be able to move to its site of recognition and action. In the case of hormones the site of perception may be a different organ or tissue, with the signalling compound being carried by the vascular system of the organism.

The production of insulin on the other hand is more akin to a recording. Insulin is encoded for by a single gene, giving rise to a single protein, referred to as pre-proinsulin. This is heavily modified, primarily through cleave events, to produce the active insulin molecule which comprises of two polypeptides. This "ready to use" insulin is then stored in vesicles in the cell until required. This is like a musical recording, the music is created and then stored, sat in its CD case, or as an MP3 file, awaiting to be played. On demand insulin is released by the fusion of vesicles to the plasma membrane in the islets of Langerhans and is released to the outside.

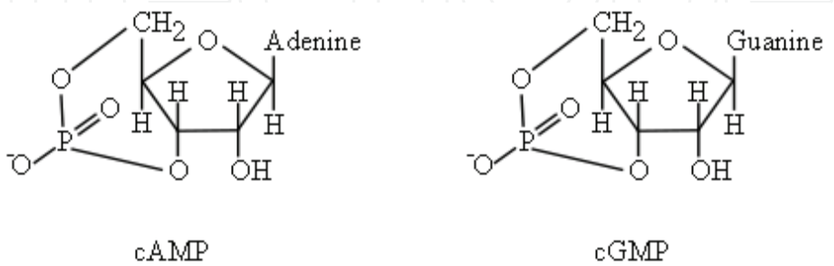
5. Uniqueness of signals

Signals used by cells have to be specific and often are unique so that their presence does not get confused with another. If a signalling molecule needs to provoke a particular response it is vital that the cell's machinery recognises the presence of that specific molecule. If there was doubt then the cell may mount a response in the presence of the wrong molecule. A good example here is role of the molecules cAMP and cyclic GMP (cGMP). As can be seen in Figure 4, at first glance both these compounds look very much the same. Both have a ribose ring, a cyclic phosphate group and an added base unit.

However, the base is different in each and therefore a cell can recognise them as different. Indeed, different enzymes make them, adenylyl cyclase produces cAMP from ATP and guanylyl cyclase makes cGMP from GTP. Downstream they are recognised as separate compounds too. cAMP controls protein kinase A, while cGMP controls amongst other things protein kinase G (Figure 5).

Musical instruments are the same. Take a quick glance at a viola, and then at a violin, and they look the same. They have the same basic shape and the same basic parts. But they are different. In an orchestra they will play different music, at different times perhaps, but what is important here is just like cAMP and cGMP, a violin and a viola have their own distinct roles and parts to play in the construction of the whole, despite the fact that they are outwardly so similar.

There are occasions when cAMP and cGMP can have similar activities, and in some cases both are removed by the same phosphodiesterase. Does this mean that our analogy breaks down? Perhaps not, as if pushed different string players can pick up alternate instruments and allow the orchestra to continue. If a violin player gets ill, a viola player can often step up to the breach to fill the gap.



cAMP cGMP

Fig. 4. Structures of signalling molecules can be very similar and yet unique. Here, the structures of cAMP and cGMP are given as examples, but they have very different signalling roles, controlling different proteins for example, that is, cAMP-dependent protein kinase and cGMP-dependent protein kinase respectively.

6. Domains and common features

In the discussion above it was argued that instruments may be similar but unique. However, there are often quite diverse instruments which share common mechanisms or structures. In signalling many proteins may also share common structures, with those structures having similar roles within the protein. A good example here is the EF hand (Lewitt-Bentley & Rety, 2000), which binds and causes a conformational change in a protein in response to changes in the levels of calcium ions in cells. EF hands can be found in a calcium controlled kinases which are able to phosphorylate downstream proteins, but EF hands are found in a wide range of other proteins too, for example the DUOX proteins involved in reactive oxygen species metabolism (Lambeth *et al*., 2007). Although there might be subtle differences in the EF hands in different proteins the structural domain is still identifiable as being an EF hand, having the same basic function but being involved in a proteins which when taken as a whole have different functions in the cell.

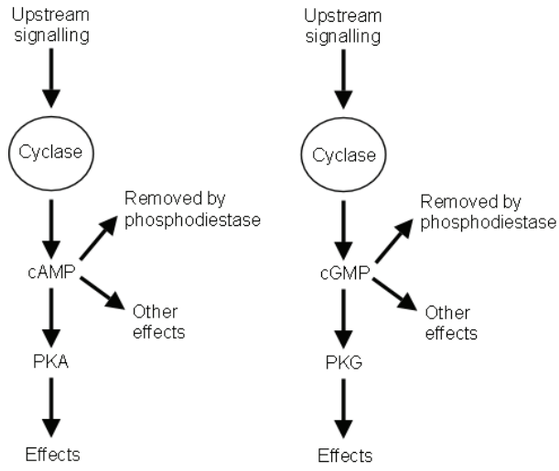


Fig. 5. cAMP and cGMP pathways are very similar. As well as cAMP and cGMP having very similar structures, if drawn in a simplistic view as shown here the signalling pathways in which they are involved is also very similar. Both are produced by cyclases, both are perceived by protein kinase, and in fact both are removed by phosphodiesterases. Both can have other effects and if viewed in more detail there are significant differences in their pathways. Importantly, cAMP and cGMP are involved in specific signalling, despite the similarities. PKA: cAMP-dependent protein kinase; PKG: cGMP-dependent protein kinase.

Therefore many signalling proteins have domains which are similar to each other and to continue our analogy musical instruments are often the same. An idea is repeated, but perhaps has a slightly different role. Consider keyboards on pianos and organs. The idea of having a set of keys which can be pressed can be found on a whole range of instruments, including different types of piano, electric keyboards, organs, harpsichords, accordions, melodicas and many others. Beyond the keyboard the mechanisms may be very different. A piano uses hammers to strike the strings, an organ opens valves to control air into pipes and so on. But the keyboard is a common feature or common structure, like the domain of a protein. And just like the EF hands discussed above, the keyboards in these different instruments may be subtly different, but they are still recognisable as being keyboards despite the overall instruments being quite different, both in shape and the type of music they play.

7. Making up a signalling system

Cells in an organism have the same genetic background, that is, they contain the same genome. The genome will encode for all the proteins which are possible to make in that organism, but different cells will have their own unique complement of proteins. Some cells will express genes for a particular signalling pathway, and others won't, perhaps having a different set of signalling proteins. Some cells will need receptors for a selection of hormones or cytokines, but other cells will have no requirement for the recognition of those extracellular signals and therefore will not express those receptors.

In music the genome is perhaps all the instruments that would be available to someone who wishes to form a group of musicians. There is a vast array of instruments available in, for example, the UK and this could be seen as the "music genome" for that country. The "music genome" for perhaps China or a Far East country may contain other instruments not commonly found in the West. So where ever a person is based to create a group of musicians they will have a "genome" to draw from, just as the cell has a genome containing the genes encoding cell signalling components to draw from. Different places could be viewed like different organisms, having different genomes, although often related. But no cell, and no music producer, would wish to enlist all the possible players. An orchestra conductor will take a wide range of instruments, from violins to kettle drums. A pop group producer may take a couple of guitars and a set of drums and little else. It is the vast array of possibilities that allow a cell to tailor its complement of proteins to allow the signalling that it needs, just as a music group will tailor its array of instruments to create the sound it requires. The cell will be able to respond to a particular group of extracellular signals while the leader of a group of musicians will be able to play a specific selection of music.

8. Receptors and their specificity

Cells are bombarded by signals all the time. It does not matter if it is a single-celled organism or a complex multicellular organism. Outside of the cell will be environmental factors such as salinity, pH, temperature, osmolarity, but on top of these will be the likely presence of compounds such as pheromones, hormones and cytokines. Therefore the cell has to be able to "decide" which it will recognise and mount a response to. The job of such a decision rests with the receptors that the cell has. If the cell synthesises the correct receptor and places it at the right place at the right time then the cell will be able to recognise and respond to the correct signal.

At the start of a practice session for an orchestra the conductor will arrive with all the scores for the piece of music which they intend to play. There will be a score for all the different instruments. The conductor generally has a score with all the parts, and s/he is like a cell which can recognise all the music. However, it would be a waste of time and effort to give such complex scores to all the musicians. Also it would make playing the music extremely unwieldy. With all the parts of the music on the score there is only a short section of notes on any page that can be seen and the musicians would be required to turn the page extremely often. This is fine for the conductor, but the musicians need to be playing, not turning pages. It would be a waste of time and effort for a cell to make all the receptors it is capable of making, that is, having the whole score. What would be the point of making a receptor for a protein hormone that it would never encounter? It would be a misuse of precious materials and space to synthesis such a receptor that will never be used. Therefore the conductor, just like an organism, ensures that each musician has the appropriate score, just with their own music to play.

This analogy can be taken further if the musicians themselves are thought of as receptors. What happens at the start of the practice session? The scores are handed out and each musician will look at the score and confirm that it is the right part, if only silently in their mind. A cello player will only wish to receive cello music: if they take violin music for example it will be in the wrong cleft and probably not able to be played. Violins not only have to get music for the violin but have the right one, being either in first or second violins. If a musician gets the wrong music they will not be able to use it and give the response that the conductor is hoping for. The musician will remain silent, even when they are supposed to be playing, like a cell receptor in the presence of the wrong ligand. It is not uncommon for musicians to return music and ask for the correct score like a receptor rejecting a ligand and leaving themselves free for the arrival of the correct ligand onto their music stand so cellular harmony can be obtained.

9. Single instruments playing a simple string of notes

Cell signalling is often presented as a neat array of components all in a line, as depicted in Figure 6A. In fact Krauss said: "The classical view of signalling pathways has been that of sequential transmission of signals in a linear signalling chain". This would be like listening to solo instruments, playing a linear line of notes on a page. Some representations of cell signalling show little else, making the systems look simple and easy to understand. But just as we don't often listen to single instruments, unless listening to a sonata perhaps, cell signalling is also a complex mix of many players, all adding to the harmony at the same time. As Krauss goes on to point out, signalling is far more complicated (Krauss, 2008).

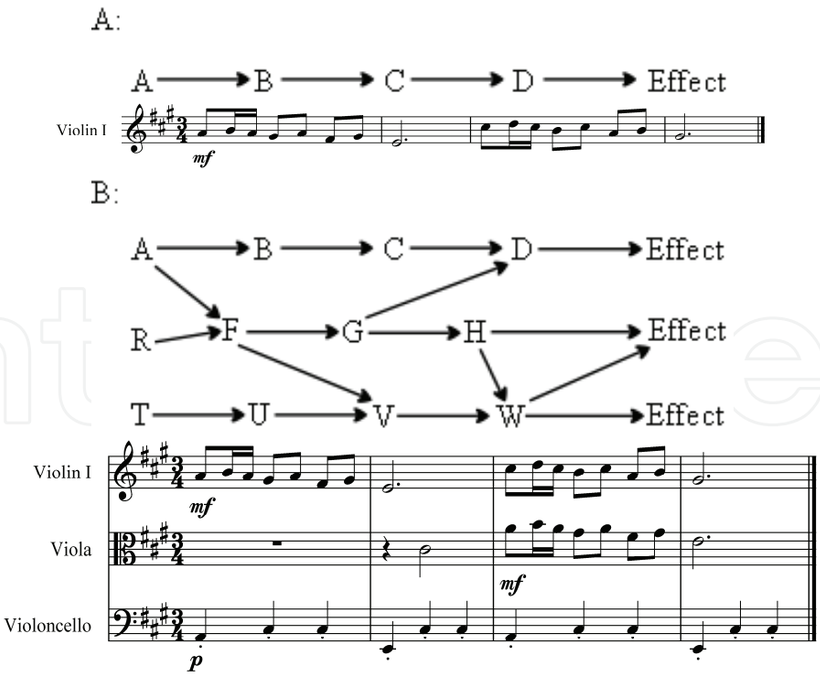


Fig. 6. Signalling pathways are often depicted as a single series of components in a line, akin to a single line of music (A). However, they are usually much more complex, more like several instruments all playing at the same time (B).

Therefore cell signalling should be thought of as a group of instruments and voices, all competing for attention at the same time. Perhaps it is more like depicted in Figure 6B. Just as in a musical group, not all these musicians need to be in action all the time, and in fact it could be rather boring if that was the case. But they will all be there on stage, awaiting their cue from the music, always ready for action, but only acting when needed. In a cell the situation is the same, many signalling components will be quiescent until they are drawn upon to play their role in the control of the cell.

10. Degeneracy

It is often a puzzle in molecular biology that proteins may be able to replace each other. Perhaps an inhibitor has been added which is supposed to remove the functioning of a cell signalling component, but the effect is far less than anticipated. In knock-out or knock-down studies, where the expression of a protein is completed ablated, or severely reduced, then the cell sometimes shows little effect (see Colucci-Guyon *et al*., 1994 as an example). In a cell signalling response, again often far less than anticipated is seen than from the theory (see Zhang *et al*., 1994 as an example). In such situations the most likely scenario is that proteins are replacing each other when needed, and protein function is said to be degenerate.

If proteins can replace each other in function can we again invoke a music analogy. The leader of the orchestra is a very important position, often helping and advising the conductor during practise sessions, but during the concert they are not redundant when it comes to control either. Like a signalling component in cells, the leader will be signalling to the rest of the violins when to start playing, so that the whole section plays together and sounds like one. However, what happens when the leader breaks a string. Violin strings are under a large amount of tension and break quite often. If the leader's violin breaks, does the orchestra have to stop. In reality, especially in a rehearsal, it probably would and a new string would be rapidly fitted. But if as in a cell, waiting for a response is not a pragmatic option and the orchestra has to continue then another violin player, probably the one in the second seat next to the leader, will take over and allow the orchestra to continue. One musician, just like the cell's protein, will take up the important role vacated by the other.

Other scenarios in music also can be envisaged. Often musicians can play more than one instrument, and especially in non-professional orchestras and groups it would not be uncommon for one player to take the place of an absence colleague. This would explain why the absence of what was thought to be an important player, or protein, can be seen to not have a devastating effect on the harmony of the music group, or cell.

11. Multiple functions of some proteins

It has been recognised that proteins often have more than one role and are said to be "moonlighting" (Jeffrey, 2009). Here, as well as proteins being able to cover the roles of each other as in degeneracy, some proteins have other very disparate roles.

Some proteins had roles discerned many years ago only to have new additional roles assigned to them more recently. A good example here is cytochrome *c* which was for many years assigned to a redox role in the mitochondria, only later to be found to be instrumental in controlling apoptosis (Figure 7. Reviewed by Jiang & Wang, 2004). Glyceraldehyde 3-phosphate dehydrogenase is central to glycolysis, but it too has now been assigned cell signalling roles, in particular as a protein which translocates to the nucleus to control gene expression (Tristan *et al*., 2011).

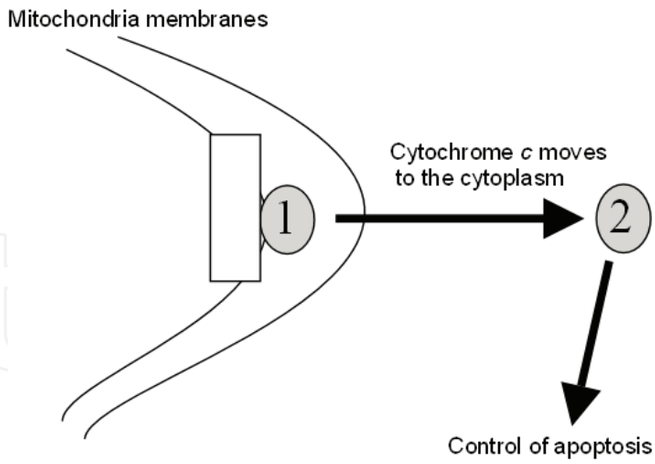


Fig. 7. Cytochrome *c* has more than one function. Cytochrome *c* is normally found in the mitochondria. It resides associated with the inner mitochondrial membrane, where it acts to shuttle electrons from Complex III to Complex IV. However, there is a signalling pathway which leads to cell suicide, or apoptosis, in which cytochrome *c* leaves the mitochondria and moves into the cytoplasm. Here it interacts with the caspase system which leads to ultimately to cell death. Therefore cytochrome *c* has two very distinct and disparate functions.

Musicians and their instruments are like such moonlighting proteins. They may play a violin, but in fact such instruments can be used in multiple music genres. During the day the violinist may be in an orchestra, but some evenings may be playing jazz in the local bar. As with the proteins, their roles are not fixed, and translocation from one venue to another will allow them to partake in a new role. Furthermore, many if not most musicians are experts at more than one instruments. Therefore if an orchestra is short of a viola player, then perhaps a violinist can take their place. Or the change of instrument can be more dramatic, with a flutist can take over on the kettle drums. Just like many proteins, temporal and spatial location of the player, and the interactions in which they may partake, may dictate the exact role they play at any moment in time.

12. Subtle changes make a big difference

In signalling systems there are many components all vying for attention, and to initiate a response. However, even though it is individual components which are studied in many cases, the overall response of the cell will be dictated by the sum of the signalling which is taking place, an idea modelled by Rachmilewitz & Lanzavecchia (2002). Even so, within this holistic approach it needs to be realised that subtle changes in the levels of some signalling components can give a large effect even if there is no change in other proteins and molecules. Certainly some signals have been described as dominant over others. An example here would be a paper by Reya and Clevers (2005) who write "Current evidence indicates that the Wnt cascade is the single most dominant force in controlling cell fate along the crypt–villus axis". Therefore, a small change in a dominant pathway would initiate a significant response regardless of the activity of less dominant pathways.
Music is often like this, with the single notes in amongst many others having a profound effect. If a pianist plays a major chord, perhaps a C, E and G, to produce a chord of C major, the effect is recognisable, and being major will sound cheerful. However, keeping the C and G the same,

but lowering the tone of the E by a semitone to E flat and the chord becomes minor. This is a significant effect. One note amongst the three has changed by a relatively small amount, but the chord is now recognisably different, and the resultant sound has gone from a happy major to a rather sad minor. A small musical change, with a large result. Beethoven uses the alteration of one note in amongst many to great effect in the first movement of the "*Moonlight Sonata*" (Piano Sonata no. 14 in C sharp minor - Op. 27 no 2) for example.

13. Background, volume and thresholds

Signalling in cells needs to take place in the presence a background level of "signalling noise". Cells are bombarded by extracellular signals all the time, whether from the environment of the organism or from other cells of the same organism. The demands on a cell will be constant and varied in many cases. Therefore, if a major response is needed, the signalling that is invoked needs to be "heard" above the noise of the rest of the activity of the cell.

Most signalling systems will in fact be in a state of equilibrium. Often levels of signalling components are measured, perhaps before and after a treatment. However, rarely do the levels of activity, levels of signalling molecules or levels of phosphorylation go from a base level of zero to a higher level. In the vast majority of cases the levels rise from a low level to a transiently higher level. Therefore researchers define threshold levels for signals, (for example Pereyra *et al*., 2000).

How individual signals get heard may be liken to phrases in the orchestra when one instrument temporally is dominate and can be clearly heard, especially an instrument such as a kettle drum. In music there are often many instruments play all at the same time, and often it is hard to discern the exact contribution of any one instrument. The holistic effect may be pleasing but the parts played by individuals are assumed to be part of the whole. However, one instrument can dominate over the others and be heard above the rest. Perhaps a trumpet is playing a strident part. It will be heard above the other hundred instruments which make up the orchestra. And the audience will follow the trumpet, the tune from which will carry the music and the mood. Cells will have a similar system. Many signals are all contributing, but the arrival of a new hormone may need to dominate. A pathway may be activated, and the activity of the players in that pathway will reach a threshold allowing them to have their effect above that of the other signalling components, which will after all be carrying on doing what they were doing before. However, transiently, the pathway with the "volume" which is dominant will be able to invoke the cellular response needed.

Some instruments such as a bagpipe rely on a background tone, or drone (Nordquist & Ayers, 2009). The highland bagpipe has a tonic note (that is the base note of the scale) of A. Therefore, the other notes are played over this, but the tonic gives the constant tone to the music. It is the other notes which will dominate to give the tune and harmonies. In cells there are various parameters upon which activities and functions of proteins and signalling components will need to contend. In cellular compartments pH is crucial, but as well as this there is the redox state of the environment. In the cytoplasm for example, there is a high concentration of reduced glutathione which will endeavour to maintain the redox state relatively constant (Schafer & Buettner, 2001). This is important because proteins contain reactive side groups which may be affected by the redox of the medium in which they function. Such groups include the thiol groups of cysteine residues for instance. Here, two cysteines may react together in an oxidation reaction to create a disulphide bridge which may stabilise the protein. Alternatively they may react with signalling molecules such as

nitric oxide (to be S-nitrosylated) or hydrogen peroxide (to be oxidised). Disruption of the redox state of the cell towards the oxidised state is referred to as oxidative stress, a condition of cells with is extremely important not only to control cell function but also to regulate processes such as apoptosis. Oxidative stress has been implicated in numerous diseases, including degenerative disease (Kadenbach *et al.*, 2009). Therefore it is extremely important for this basal redox state to be maintained, much like a basal note of the bagpipe. It needs to be there, allowing continuity of the harmony of the cell. However, there does need to be the involvement of signals such as hydrogen peroxide and nitric oxide. It may be that the basal redox state in some cases maintains the thiol groups in a state to enable compounds such as nitric oxide to react and have its effect. This would be like the pitched notes on the bagpipe being strident above the background tonal level. On the other hand, if the background is disturbed, perhaps during oxidative stress, such thiols would have already reacted with for example hydrogen peroxide and be no longer available for a reaction it would normally partake in. A disruption of the basal background harmony has altered the effect of the other signals, and the overall effect is quite different. For normal signalling to resume, the background "tonal" redox state would need to be restored.

14. Timing and phasing: Oscillations and waves

One of the intriguing aspects of cell signalling is the timing of the signals and how they fit together temporally. To get a full understanding of signalling needs a full appreciation of both the spatial and temporal aspects of any signal, but particularly how they might be working together in time and space. Early work in this area concentrated on calcium ion signalling, and it was reported that calcium ions were not only altered transiently in some systems but this transient change in ion concentrations actually followed an oscillating pattern. A superb example of this is shown by Alberts *et al.* (1994). Here, the oscillations are dependant on the concentration of the initial signal added. It is not the amplitude of the change which seems to be important in this signalling, but rather the frequency of the oscillations. However, temporal fluctuations on the concentrations of signals are not unique to calcium ions. The biphasic nature of other signalling systems has also been reported, for example with reactive oxygen species (Bleeke *et al.*, 2004) and also with insulin signalling (Rorsman *et al*., 2000). If hydrogen peroxide levels are followed for example, they increase quickly but transiently, but after a period of relatively low activity the levels once again rise, often to be sustained for the second period. This may be reflected in levels of other signals too, such as nitric oxide. Therefore, at any moment in time the levels of signals may be rising and falling, and it is probably the combined nature of such changes which brings about the desired response in the cell. It is pattern of change which should be considered, rather than the individual changes which might be being recorded.

Music is often written in a pattern. As discussed above, Lane likens biological variations and patterns to musical variations (Lane, 2010). But musical patterns are often phased too. A prime example here is the fugue. Oxford Dictionaries describe a fugue as being written in such as way that "…a short melody or phrase (the subject) is introduced by one part and successively taken up by others and developed by interweaving the parts." A superlative example of such a work is the fugue in the *Toccata and Fugue in D minor*, BWV 565, by Johann Sebastian Bach.

Cell signalling in some cases needs to be thought of in this manner. Hydrogen peroxide and nitric oxide can be considered as two lines of music, one being interwoven with the other. One

rising and falling in unison with the changes in the other. But of course it would be naïve to think in these terms for just two signals such as these. Both nitric oxide and hydrogen peroxide can impinge on calcium signalling, so phasing of changes in calcium ion concentrations will need to be considered too. But a myriad of other signals will be employed at any moment in time in a cell so the overall response, or set of responses needs to be orchestrated by the phasing and overall shifting pattern of signals being employed by the cell.

15. Setting up for the future

In music there are often times when the phrasing and harmony just does not sound quite right. This is usually very transient and the harmonies resolve very quickly. Perhaps a composer has asked for a F and a G to be played together. If they were the adjacent notes the resulting discord would be very obvious, but often such notes are played with two or three octaves between them – in those cases the discord is not so blatant. However, often that harsh nature of the discord will mean that when the music does harmonise the end result is more pleasing than it would have been without the disharmony. The composer has set the scene for the final resolution. Again using Beethoven as an example, he does this to great effect in the "*Moonlight Sonata*", where the listener is treated to slight disharmony and one is waiting in anticipation for the resolution, which when it comes is delightful. It brings depth and feeling to the work. Therefore the composer is setting up for the future, ensuring that what subsequently arrives results in a success.

Cells need constantly to be setting the scene and making sure that they are ready for the future. And of course cell signalling is the key to doing this. Signalling often leads to adaptation, where the cell sets itself up for future possible events (Neill *et al*., 2002). Music often sets the scene in a strident and discordant, or stressful, way to allow for future harmony. In cells exposure to one stress can lead to cells being able to cope better with subsequent stress in the future, and not only to the same stress. Temperature stress in plants for example can lead to adaption to future stress by other abiotic and biotic stress factors. Instead of viewing sub-lethal stress as a negative thing in cell signalling perhaps we should be more like the composer who is prepared to chose a discord to ensure the future has a better outcome. The composer is adapting our ear, just as cell signalling is adapting the functioning of the cell for future events.

In cell signalling adaptation and preparing for the future may require long term activity, and will no doubt involve the control of gene expression with an alteration of the complement of proteins in the cell. Perhaps the cell will alter its levels of certain receptors or signalling proteins, and this will enable the cell to have a faster or more tailored response in the future. This would be like a disc jockey in the night club being asked for a certain genre of music, but realising that he didn't have it. There would be a period of short term stress. Instead of being caught out in the future, a trip to the music shop would ensure that he would be "adapted" for future requests, so lessening the chance of stress, and also allowing alternatives to be played which may relieve an otherwise stressful situation. Our cell signalling would "take a trip to our genome" and so ensure that they are ready for future "requests" from their environment.

16. Signalling dysfunction

Dysfunction of cell signalling can have catastrophic consequences. This is certainly one of the main reasons why the topic needs to be more fully understood. Dysfunction can lead to

either the lack of functionality or indeed too much activity, with either situation being undesirable. If insulin signalling is taken as an example, a dysfunction of the insulin receptor would mean that the arrival of insulin at the cell surface would not be recognised and no insulin response by the cell would be mounted. Obvious effects of such a dysfunction are conditions such as diabetes. One the other hand, if the G protein Ras is taken as an example, mutation of the coding for amino acids at position 12, 13, or 61 in the sequence leads to a protein which has impaired GTPase activity and therefore can not be turned off (Figure 8). This leads to the signalling pathways in which RAS is involved being in the permanently active state, regardless of the lack of continued initiation of the signalling pathway. *RAS* mutations are found in about one third of human malignancies (Riely *et al.*, 2009). These are just two examples and there are many more, highlighting the importance and impact of correct cell signalling.

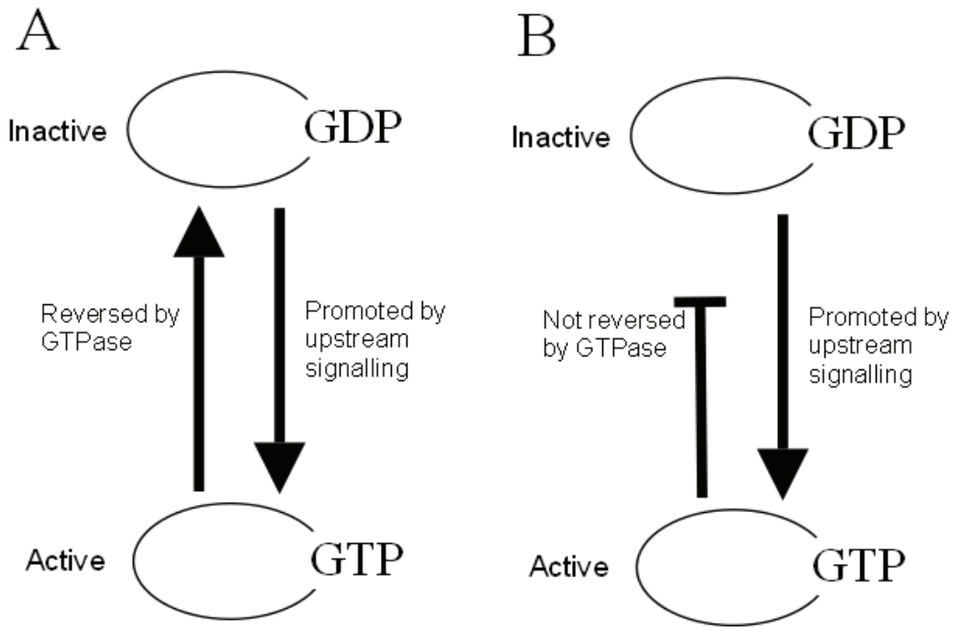


Fig. 8. G protein dysfunction can lead to continuous signalling. G proteins can be thought of as being molecular switches, with an "on" and an "off" state. In the inactive state they are bound to GDP, but on activation this is exchanged for GTP, so leading to a conformational change in the protein which allows it to signal (A). The GTP bound form of the G protein will then signal downstream to the next effector in the chain. In the case of the G protein Ras, the next signalling component in the transduction pathway could be the protein kinase Raf. To then inactivate the G protein its intrinsic GTPase activity will convert the GTP back to GDP and inactive the protein – through a reversal of the conformation change. However, in proteins such as Ras, a mutation can disrupt the GTPase active site so stopping the conversion of GTP back to GDP (B). In this case, the protein will continue to be bound to GTP, and continue to be in the conformation that signals. Therefore, even if all the up-stream signalling is reversed or halted, the G protein will continue to signal downstream regardless. Because Ras is often on pathways which are invoked by growth factors, continuous G protein signalling can lead to a continuous "grow" signal, and hence lead to tumour growth and cancer.

Dysfunction can and does happen in music too. The discussion above emphasises the fact that many cell signalling events will be taking place in the cell at the same time. There may be many effects, often in different parts of the cell. However, there should be minimal interference of one pathway over the other if they are controlling completely independent effects. At many music venues in recent times there may be several events taking place all at the same time, and the Glastonbury Festival is a good example. People need to listen to the band of their choice without hearing the others in such a way that it disrupts their enjoyment. However, if one band starts to dominate, or the equipment on one band loses its volume, then the effect that the festival envisaged will be compromised, just as the overall signalling network of the cell would be compromised. An example of this would be signals moving into a cell through the gap junctions. The signalling of one cell may overwhelm the signalling in one of its neighbours if second messengers move on mass through the gap junctions. Clearly there needs to be control of such movement and gap junction function and regulation is clearly important to understand (Evans and Martin, 2002).

Although it is less common now physical recordings can cause problems with both vinyl records and CDs able to "jump". This can render the music so bad that it can't be listened too. Other equipment can fail too, including digital instruments and amplifiers. But even more classical equipment can have problems. A sonata played on a piano with a broken key or hammer may make the music very poor. It may not stop the piece being played altogether, and the musician may be able to continue. However, the concert is unlikely to get good reviews and both the musician and venue may struggle to have a future event. Just like in a cell, a small dysfunction may render the longer term future to be in doubt.

17. Future and evolution

It would be naïve to think that cell signalling has evolved to the point where it will evolve no further. Organisms continue to evolve and the proteins involved in cell signalling will no doubt evolve too, and certainly will not stay the same for eternity. Likewise it would be foolish to think the same about music and instruments.

Over billions of years since life began, cell signalling proteins have mutated and changed to give the polypeptides that we can find today. Since the creation of the first cells some form of signalling was required, both to sense the environment of the cell and to coordinate adaption as the world changed. From an oxygen free atmosphere to the present climate of Earth cells and their signalling have had to adapt along the way. They will continue to change, adapt and no doubt the proteins involved in signalling will increase in number in the future. Perhaps an example of such a change can be seen with the enzyme nitric oxide synthase (NOS). Very recently a NOS has been characterised from a very primitive green algae *Ostreococcus tauri* (Foresi *et al*., 2010). Perhaps this photosynthetic organism inherited its gene for this enzyme from a more primitive cell, one which gave rise to both plants and animals. This is likely as the *O. tauri* amino acid sequence is 45% similar to that of a human gene for NOS. Therefore, the human gene has changed considerably compared to the *O. tauri* gene over time. Perhaps more striking is the fact that although *O. tauri* is a primitive plant, higher plants do not seem to have a form of this NOS gene at all. Either it has been lost altogether, or it has been mutated to a form which has yet to be identified. Either way, evolution has been hard at work on this gene, and will no doubt continue such work into the future.

Mutation and duplication of gene can lead to families of proteins. Certainly in signalling families of protein isoforms can be recognised, some with added domains, some with extra

phosphorylation sites and some in truncated form. Good examples are phosphatase proteins that remove the phosphate groups from proteins (Cohen *et al.*, 1990).

Musical instruments also evolve, and in many ways in a similar manner to proteins. Some have certainly been around for a long time, but even those that form part of current orchestrates are different from those used by great composers such as Mozart. Furthermore he would never have imagined the possibility of an electric violin, but today his music is often played on such an instrument. Music itself evolves, with successive composers building on the work of those who went before them.

Instruments have changed over the years in a way that resembles that of proteins. Protein isoforms can be created when a gene is copied so there are two versions, and then those genes mutate after a period of time to two separate genes which are able to be characterised, and they would give rise to different but related proteins. Musical instruments are the same. A violin is like a copy of a viola, except one is bigger and plays different notes. Copy it again and make it bigger still and a cello is created, and so on so there is a family of instruments which are recognisable as being related, and yet they have different roles. They could be thought of as isoforms perhaps, just like proteins. Using the piano as an example and again one can see "isoforms" which are all recognisable as pianos, that is the concert grand, the baby grand, the upright, the studio piano and so on. Over the years the piano has been adapted to the place it needs to be placed and the audience it is aimed at. There have formats which are no longer seen, like genes which have disappeared during evolution, and there are new versions being developed and used. There now seems to be a vast array of electric pianos and electronic keyboards, with the idea of using a piano keyboard layout being copied and mutated to develop new instruments.

Music and the instruments used to create it will continue to develop and evolve, just as the proteins which are involved in cell signalling. Especially in the advance of climate change, organisms will need to adapt and it will be cell signalling which coordinates such changes, but the signalling pathways will change too. The future will see the development of new cellular components, and no doubt new musical instruments, especially as new digital technologies are adopted. Not all changes will be beneficial, with mutations in genes no only allowing the future evolution of species but creating dysfunctional proteins along the way causing disease in individuals. No doubt not all new music innovations will be successful either, and the future will be littered with new proteins and musical instruments abandoned by nature and the music industry respectively.

18. Conclusion

Cell signalling is both enormously important to the understanding of how cells works and immensely complicated. Therefore ideas which can be used to aid in the teaching and study of the subject would be extremely helpful, and an analogy is often a good tool. Music initiates cell signalling events in organisms, but music terminologies are often used to explain aspects of cell signalling. However, music as an analogy for cell signalling events can be an interesting and useful way to look at the principles of signalling and transduction pathways. Such an analogy will be useful to those teaching and studying cell signalling.

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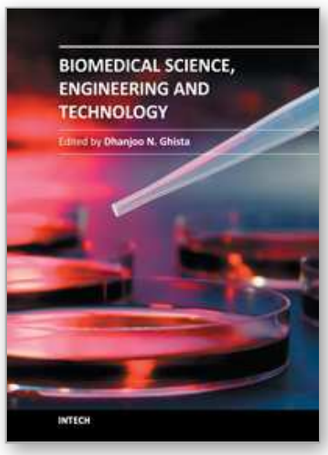

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University Campus STeP Ri
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