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Analogies in 3D molecular visualisations: development of a cell biology animation ‘How cells move - a new interpretation of old data’

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Abstract

Cell biology and imaging technology have vastly improved over the past decades, enabling scientists to dissect the inner workings of a cell. In addition to technical limits on spatial and temporal resolution, which obscure the picture at the molecular level, the sheer density and complexity of information impede clear understanding. 3D molecular visualisation has therefore blossomed as a way to translate molecular data in a more tangible form.

Whilst the molecular machinery involved in cell locomotion has been extensively studied, existing narratives describing how cells generate the forces that drive movement remain unclear. Polymerisation of a protein called actin is clearly essential. The general belief in the cell migration field is that actin polymerisation's main role is to push the leading edge of the cell forwards, while the rest of the cell follows passively. The cell migration & chemotaxis group at the CRUK Beatson Institute propose an alternative hypothesis, in which actin filaments constitute cables. Motor proteins pull on these cables, causing them to behave like the treads of a tank and drive cell movement.

This article describes the development of a 3D animation that uses analogical reasoning to contrast the 'tank' hypothesis for cell locomotion with the current dogma.

(Abstract = 200 words; Main text = 4466)

Introduction

Animation as a modern-day thinking and communication tool

Historically, 3D physical models were widely used in many scientific disciplines as teaching aids or ‘thinking tools’ for researchers. They demonstrate spatial relationships, provide a physical representation of abstract concepts or depict what cannot be seen, and are highly advantageous as they can be taken apart and reassembled repeatedly [1, 2].

Traditionally, model figures depicted in scientific journals are simple concise 2D representations that describe a proposed hypothesis or summarise research findings. The main aim in creating a model figure is to communicate with clarity the key messages the author needs to convey to their audience. However, a 2D schematic can often fall short when conveying molecular/cellular interactions, localisation, and structures that are highly dynamic or mechanistically complex [2, 3]. Furthermore, the rich narrative in a research manuscript can be easily lost due to oversimplification of concepts and/or the illustration being confined to a single figure [4, 5].

Whilst physical models and 2D diagrams continue to be used widely, scientists are becoming more aware of using *in silico* visual representations of their laboratory data to enhance communication of their ideas and aid learning, particularly as computer graphics and software continue to evolve [3, 5, 6]. Embedding of 3D data viewers (for structural biology and microscopy) within online research articles is steadily increasing [7].

High quality cell and molecular biology mechanisms of action (MoA) 3D animations are often commissioned by pharmaceutical or healthcare establishments to promote and explain drug mechanisms or medical procedures that are usually tailored towards a lay audience. Whilst many MoA animations have a cinematic quality that is very engaging, many are not ‘anatomically’ correct and hence this is a niche that microscopists in collaboration with 3D animators may be able to fill [8].

A greater number of scientific journals are now welcoming animations created by the authors to communicate their findings [5]. Animations within articles or on lab websites which succinctly express the research done by a particular group can markedly enhance engagement with the reader [4].

Molecular visualisation advances

Improvements in structural biology techniques have enabled better understanding of the ‘molecular sociology’ of cells (how proteins are spatially arranged and interact to perform cellular functions) [9, 10]. In addition, advances in computational power and new methodologies have enabled molecular dynamics simulations to be more widely used to examine protein mechanics of large macromolecule assemblies [11, 12].

Confocal microscopy techniques have also undergone significant improvements in the past few decades, including better hardware (lasers and detectors), more sophisticated software that enables 3D time-lapse, faster imaging speeds, and accommodation of large datasets.

These advances in experimental biology have warranted more sophisticated visualisation of findings. It has become possible to create high quality movies based on real data [5, 13]. Raw confocal data can be reconstructed using a number of free and commercially available packages such as Amira (FEI), Imaris (Bitplane) and 3D Slicer, which can subsequently be exported into 3D animation software such as Maya or 3ds Max (Autodesk) [8]. There are however limitations to using these software to extract meshes from large volumetric data sets, such as high noise-to-signal ratios which consequently require significant manual clean-up [14].

The RCSB Protein Data Bank (PDB) (<http://www.rcsb.org>) is a free worldwide resource with numerous 3D visualisation viewers that allow scientists to access data on biological structures [15]. PDB IDs can be exported from this vast repository to various 3D modelling programs enabling users to create visualisations that are structurally correct, eliminating the need to model molecules from scratch.

Commercial 3D animation software packages usually tailored towards the entertainment and game industries, are now becoming more widely accessible so that scientists can import their own data to create simulations and animations [4]. Some 3D applications have plugins such as ePMV [16], BioBlender [17] and Molecular Maya [18] that enable molecular meshes to be imported from databases that can be adjusted and animated like any other model.

Although the availability of molecular plugins has bridged a gap between experimental data and visualisation, good renderers such as Vray, Arnold, and Mental Ray are necessary in the production process. The modelling and rendering tools in 3D animation software can be difficult for novices, and may continue to discourage scientists from creating their own visualisations [4, 5, 19].

Art of analogy

Animations depicting complex cell biological processes or hypotheses can often be more intuitive for an audience to follow than text or a 2D diagram. However, some caution must also be taken when creating imagery for education, outreach or peer-peer communication purposes [20, 21]. Balance is crucial so that the viewer can trust the accuracy of the information, but also not to be over- or underwhelmed by a surplus of detail or oversimplification respectively. Arguably, some artistic licence may be acceptable if generating interest through outreach is the goal, or for teaching a general view of a scientific concept [2, 22].

When creating visualisations for communicating to scientists in the research community, more detail may be required, but whether that can hinder good storytelling is debatable. Sometimes selective exclusion of information is needed such as simplifying the true nature of a crowded cellular environment, modifying the timescale of processes which may in reality be lengthy or extremely rapid, and distortion of scale to focus on objects of interest within the scene [13, 21, 23, 24]. Furthermore, researchers may be concerned that a hypothetical model may unduly influence viewers into thinking the model is actually replicating experimental data or is a true reflection of reality, and therefore they must be carefully designed [2, 25].

Cell locomotion

Through advances in microscopy, biochemistry and molecular biology, the major proteins and signalling events involved in cell locomotion have largely been identified. However, elucidating precisely how these cellular components co-ordinate to work as an integrated system and generate the required forces for motility still remains unclear.

A translocating cell has to exert force to overcome the friction of the substratum and the surrounding liquid. To achieve this efficiently they acquire a polarised morphology (extending protrusions at a restricted front with concomitant retraction at the rear) [26]. The collective actions of two self-assembling cellular machinery that undergo cycles of growth and turnover - the actin cytoskeleton and cell adhesions - are crucial to power cell locomotion. Actin filaments and various regulatory proteins work as force generators, whilst cell adhesions provide a physical link between the substrate and the cytoskeleton [27].

Analogies to depict hypotheses of cell locomotion

Many studies have shown that the actin cytoskeleton is essential for lamellipodial and filopodial protrusion [26-28]. However, the question of whether actin polymerisation is the driving force for cell locomotion is still debated. Most current authors describe the primary role of actin polymerisation as driving the edge of the cell forwards, whilst the rest of the cell body follows passively [28].

Some key experiments that led them to this hypothesis came from research done using simple model systems to study actin-based cell motility involving the bacterial pathogen *Listeria monocytogenes* or biomimetic systems (synthetic spherical beads or phospholipid vesicles). *L. monocytogenes* are rod-shaped bacteria that infect mammalian eukaryotic cells, hijacking the host's own actin polymerisation machinery and energy to move within the cell [29].

The propulsion of *L. monocytogenes* or beads due to polymerisation of actin filaments is also thought to be the mechanism responsible for pushing a cell's leading edge membrane forward, therefore providing the force to generate locomotion. Many researchers believe the cell body moves as a consequence of being 'pulled' by the leading edge, with cell adhesions weakening and acto-myosin contraction at the rear [28]. An analogy is that of a two-step movement by a climber using their hands to grip and then subsequently shift the bulk of their body as they scramble up a mountain.

Whilst there is plenty of data in the literature that has explored the assembly of the actin cytoskeleton and adhesions at the cell front, current explanations of their decomposition and recycling at the back is less clear.

The Cell Motility and Chemotaxis lab at the CRUK Beatson Institute, and its director, Professor Robert Insall, believe the existing interpretation in the literature (the mountain climber analogy) currently cannot fully explain the force generation responsible for locomotion. They present an alternative hypothesis of propulsion. Based on existing data in the literature and from their lab, the Insall group believe an animation can help to explain their alternative hypothesis, whereby the actin filaments throughout the cell provide cables for motor proteins (myosins) to pull on. A suitable analogy of their suggested propulsion system within a cell is that of tank treads, where the treads represent actin molecules.

This paper describes the creation of a 3D animation that uses analogies to communicate the distinction between the existing and new hypothesis (that the mountain climber analogy

represents a two-phase motion, whereas the tank analogy represents one smooth continuous movement). The final animation was subsequently screened to an audience with a scientific background.

Materials and Methods

Materials

The software used in the project can be found in Supplementary Figure 1A. See supplementary Figure 1B for references of microscope movies.

Sound was recorded using a Scarlett 2i2 USB microphone at the Digital Design Studio (Glasgow School of Art).

Methods

Script and storyboarding

The animation script was written in collaboration with Professor Robert Insall (CRUK Beatson Institute). A storyboard was drawn up and the animation split into 3 major scenes:

Scene 1: Introduction

- Relevance of pseudopods for cell migration
- Introduction to actin
- How *L. monocytogenes* experiments influenced the interpretation of actin's role in migration

Scene 2: Mountain climber analogy

- Explanation of how actin and pseudopods drive migration according to the majority of researchers (split screen cross-sectional views of a cell and mountain climber)

Scene 3: Tank analogy

- Alternative hypothesis from the Insall lab, whereby actin dynamics within the cell mirror the movement of treads on a tank (cross-sectional views of the whole cell superimposed on moving tank treads)

Dr Olivia Susanto (CRUK Beatson Institute) kindly provided the voice-over for the animation.

Creating model assets

The cell

The fish epidermal keratocyte was chosen as the model for the animation because it is a cell type widely used to study cell locomotion. The keratocyte cell was sculpted in Zbrush (Figure 1A).

Actin

Actin is a highly abundant protein found in most eukaryotic cells that is able to form filaments. Actin filaments (F-actin) are composed of repetitive assemblies of monomeric actin (G-actin) that form in a head-to-tail fashion so that they are helical and intrinsically polar [30].

Often when depicting mechanisms or signalling pathways in journal figures the proteins are represented as simplified shapes that bear little resemblance to their experimentally determined molecular structure. Since actin was a focal point in the animation, a suitable actin filament crystal structure available on the RSCB Protein Data Bank (PDB ID: 3B63) was chosen to maintain some basic molecular authenticity. This was imported into mMaya (Clarafi.com) so that the molecular mesh and ribbon structure could be modelled and animated (Figure 1B).

There are many regulatory and accessory proteins required to initiate actin polymerisation, regulate filament assembly, and turnover [30]. However, this level of detail was decided to be superfluous for the purposes of the project.

Mountain climber and rock face

The SuperAverageMan ztool in Zbrush (Figure 1C) was used as the model for the mountain climber. The rock face upon which the figure would climb was made in Zbrush using zspheres, sculpted with zbrushes (Figure 1D).

Cell adhesions

For a cell to move it needs to transmit force (traction) to the substrate, to do this they create adhesions complexes which form and disintegrate at different stages of locomotion [26].

A shark tooth model (Figure 1E) taken from the ZBrushCentral website: [http://www.zbrushcentral.com/showthread.php?61124-Monsters-by-skullbeast-\(John-Cherevka-s-W-I-P-\)/page14](http://www.zbrushcentral.com/showthread.php?61124-Monsters-by-skullbeast-(John-Cherevka-s-W-I-P-)/page14) was used to represent the action of cell adhesions.

Myosin II

The role of the motor protein myosin II in cell motility remains ambiguous. Cell biologists generally assume that contractile force generated by non-muscle myosin II at the rear is necessary for tail retraction events during cell locomotion [31]. To simplify this complex structure, the Gear3D ztool (Zbrush) was used as a mesh to give the impression of a molecular motor (Figure 1F).

L. monocytogenes model

The *L. monocytogenes* model was sculpted in Zbrush.

Tank

The tank model (Figure 1G) was downloaded for free from the CGTrader website (<https://www.cgtrader.com/free-3d-models/vehicle/military?keywords=soviet+heavy+tank+SMK+USSR+1939>).

Texturing

With the exception of the tank, all models were imported into Zbrush for Polypainting onto the surface and subsequently the texture, normal, and displacement maps were exported.

In some scenes the whole keratocyte cell needed to be viewed cross-sectionally to reveal the structures within. To achieve this effect without creating a new model, a grayscale transparency map was created and attached to the material in the Maya Hypershade. The map works by concealing the texture map of the model where the areas are black but maintaining the texture in the white regions.

Animation

Actin polymerisation

Actin monomers and filaments were key features in the animation and appeared on numerous occasions. Animating polymerisation involved sequential movement of single actin monomers to join the end of existing filaments at the front. Initially, a branched network of actin filaments was modelled in the scene, on to which new actin monomers were added.

Each actin monomer in a growing filament had their geometry constrained to their individual motion path and importantly the helical orientation of the filaments was maintained. The first 5 actin monomers each moved along the curve over 1 sec, so that the viewer could more clearly observe their addition to the existing stationary filament ends. The remaining monomers travelled over a 0.5 sec period; this was done so that the overall movement of the cell leading edge became more obvious (Figure 2).

Cell migration

Most cells have membrane ruffles at the leading edge as they translocate. To create a realistic effect of this flowing movement, a lattice deformer was applied to the cell. This placed a cage around the cell so that the mesh could be manipulated using the lattice vertices. The lattice applied was subdivided into 16 x 8 x 5 divisions. Over the course of the actin polymerisation animation, the lattice vertices were manipulated individually every 30 frames to create a 'natural looking' cell protrusion and ruffling motion (Figure 3).

Mountain climber

The SuperAverageMan model was rigged in Zbrush and adjusted into various poses for each of the climbing stages. They were imported into Maya where the individual poses were positioned against the rock face model. Parts of the climber's body were coloured green to highlight areas that corresponded to parts of the crawling cell e.g. extension of arms being cell protrusions, hands the adhesions, and legs representing retraction of the cell rear (Figure 4A and B).

Tank movement

Animation of the tank model was done in Maya. The treads and the individual wheels were first separated from the tank body. A single tread was duplicated and rotated to form a circle, and then attached to a NURBS primitive circle using the Wire Tool. The shape of the treads

was adjusted to resemble the original tread. The treads and wheels were keyframed and parented to the tank body (Figure 4C and D).

Tank analogy cell

The whole cell animation required multiple components moving simultaneously (Figure 5). Actin monomers needed to be added to the existing branched filaments at the front and removed by the action of the myosin motor from the filaments at the rear. Movement of the entire cell was achieved using the lattice deformer as described previously. Actin monomers were animated along new motion curves that originated from the rear to join onto the growing filaments at the front. The gear model which represented the myosin motor was animated to rotate in time to the removal of the actin monomers from the rear filaments.

The complex cycle of cell adhesion turnover was simplified by showing a change in colour of the shark teeth (Figure 5). Nascent adhesion sites called focal complexes that form under the leading edge lamellipodia were coloured dark red and animated digging into the substratum. Larger focal adhesions which remain stationary relative to the substrate as the rest of the cell body advances were pink. Focal adhesions at the retracting cell edges, that eventually detach (shown to fade away) were purple.

Lighting and Rendering

Various lighting effects, including spotlights and Physical Sun and Sky (PSS) lighting were used. All scenes were rendered in Maya using Mental ray, at HD 540 (960x540), resolution 72.0, sampling quality of 0.25.

Post-production and compositing

Adobe After Effects (AE) was used to composite all the rendered scenes, addition of any special effects, text, and the voice-over.

Various microscope movies were included to introduce the topic of cell migration. Circular masks were used to give the impression that the viewer was looking down a microscope. Masks were also used to create a split screen effect for the mountain climber analogy scene. Fading effects were used for the slow transition overlays of the tank model and the whole cell.

The final animation was rendered in AE at 1920x1080 resolution with an H.264 video compression; an audio output of 44.100 Hz, 16 Bit stereo.

Results

Development outcomes

The final animation was 3 minutes 30 seconds long with narration, and can be viewed at <https://www.behance.net/shereenkadir> entitled: 'How cells move' animation. The initial title screen appears with a cell that is used throughout the animation. An introduction to the topic of cell migration is accompanied by a series of microscope movies of real cells. The camera zooms into the 3D cell to introduce actin and an explanation of actin polymerisation driving cell protrusion (Figure 6A-E).

The next stage of the animation visualises the actin polymerisation at the leading edge and the general assumption in the field that a function of actin is to push the front of the membrane out, which is based on the *L. monocytogenes* experimental data (Figure 6F).

The final parts of the animation depict the two differing analogies about how cells move. First, the mountain climber analogy describes a widely accepted view of cell migration. Here the stills of the climber and the cell are shown as a split-screen with a slow morph between the frames (Figure 6G). Next, the Insall lab's hypothesis is explained, whereby the treads of a tank represent the movement of actin to drive cell migration. Here the tank is fully animated and the various proposed mechanisms (actin polymerisation/depolymerisation, focal adhesions, and myosin) inside the cell are revealed sequentially whilst morphing to the model of the tank (Figure 6H).

Initial feedback from experimentalists

The Insall lab was consulted throughout the production process. Overall, they were pleased with the outcome of the animation and felt it successfully presented the two analogies. The design and appearance of models (actin, cell, mountain climber, and tank) were commended. Whilst the cell was very simplified the detail of the cellular machinery was at the right level so as not to overwhelm the viewer with excess information. Most notably, the use of uncomplicated 'recognisable' meshes to represent complex cell machinery (myosin as a gear, and adhesions as shark teeth) to imply their function was positively received. Inclusion of a voice-over (spoken by a postdoctoral scientist who had been involved in generating the experimental data) was also praised. Some multimedia studies suggest that users shown

animations with narration find them far more effective at improving learning and understanding than text alone [32].

The mountain climber scene was mostly criticised because it was not animated fully in the same manner as the rest of the animation, possibly weakening the visual strength of the analogy. The climber model could have been rigged and animated in Maya, but this was not achieved due to time constraints.

Another criticism of the scene was that the behaviour of the actin filaments at the front of the cell was only visible, whereas the cell in the tank analogy showed the behaviour at the rear as well. This was a deliberate choice by Professor Insall to purposefully focus only on the front filament, because the idea was to highlight the gripping action by the forward protrusion phase (i.e. the climber's hands and the cell adhesions that appear), which many other scientists believe to provide the force for initiating movement. Although the filaments at the rear of the mountain climber analogy cell would also be depolymerising, the timing is not the same as for the cell in the tank analogy. The focus of the mountain climber analogy cell was to make it clear that climbing mechanisms consist of two distinct phases – protrusion of the front and then retraction behind, at the climber's arms and legs, whereas the tank analogy cell can work continuously. Therefore, addition of the depolymerising filaments at the rear of the mountain climber analogy cell might have added too much visual clutter.

The tank analogy cell scene could have also been improved by making the actin polymerisation/depolymerisation cycle more visually striking. Whilst the animated movement does capture the cyclical nature of the process nicely, perhaps a colour change would have a positive effect.

Lastly, some commented on the fact that the cell adhesions were present in the animation but were not referred to in the narration. In hindsight it would have been a good idea to mention them.

Animation screening to scientists

The main purpose of the animation was to communicate to the cell biology community a generally accepted existing hypothesis of cell locomotion and explain an alternative hypothesis proposed by the Insall lab, illustrating their differences, and the advantages of the new model.

Scientists working at the CRUK Beatson Institute were invited to an animation screening and feedback was acquired through questionnaires. The anonymous comments were a mixed range of opinions and some were extremely positive in their feedback. However, others questioned the science behind the Insall lab hypothesis, one could argue that promoting such discussion is the purpose of the animation.

Discussion

One of the main aims of the project was to communicate effectively new ideas, in this case an alternative hypothesis of how cells move compared with the current dogma in the field. The animation was commissioned because the two analogies were particularly difficult to comprehend when explained only on paper or verbally. Based on the feedback from the Insall lab and questionnaires following screenings to a wider scientific audience, the animation generally enhanced people's understanding and appreciation of the subject matter. The narration in the animation was positively received and set the scene for the two analogies very well. The tone of the language was purposefully not too difficult with minimal technical detail for the target audience to follow.

Most scientific papers are written in a dry and unemotional way (devoid of descriptive language) so that the focus is on the data, aiming to minimise bias. Storytelling is a contentious area when it comes to scientific writing and visual communication. Rich narratives and the use of analogy can emphasise a message and engage the viewer without bombarding them with minutiae [33]. However, one could argue they are intrinsically persuasive, and perhaps there is a danger of embellishment in order to frame a story, particularly if critical information is restricted from the audience, which raises ethical considerations [34]. A greater transparency through the use of citations of the data from which the visualisation is based is possibly one remedy [25].

The depiction of the cell and protein players was generally praised by the viewers. Although it was greatly simplified (containing no organelles, displaying only the proteins of interest, some of which were as analogies of their function), this was intentional so as not to overwhelm the viewer. Many studies have shown that consideration of cognitive load is essential when designing multimedia for learning and communicating ideas [32]. Furthermore, it would have been impractical to try and replicate the true density and scale of proteins, because the size of the actin monomers relative to the whole cell would be far too small to observe clearly in the animation. Furthermore, imitation of a more 'authentic' cellular environment would not necessarily contribute to the goals of the animation.

Investigating effective methods to evaluate analogical arguments where 3D animation is a medium is clearly necessary. A larger sample of participants and testing groups from different institutes would be worthwhile for meta-analysis in this study. In fact, it could be argued that

the scientists at the Beatson Institute may be biased in favour of the models because they may have an existing knowledge of the subject or have been to seminars by Professor Insall on the topic already. For future analysis, the participants could be assessed in their prior knowledge of the subject and then potentially categorised into different groups based on their existing level of understanding.

There are numerous studies in the literature that test the efficacy of animations for teaching purposes, however there is no general consensus on their effect on long-term memory retention, and varying degrees of improvement in examination scores [20, 35]. Many simply draw conclusions from student satisfaction surveys and rely on the outcome of test scores confined to one school. Nevertheless a lot of these studies revealed animations generally enhanced enjoyment and satisfaction. A recent study by Shahani and Jenkinson examined the effectiveness of interactive analogical models on undergraduate chemistry students' understanding of bond energy curves [36]; the data showed students failed to correct visual descriptions of energy wells. The authors suggested cognitive overload was a problem and highlighted the importance of careful design.

A 3D designer has to accomplish a fine balancing act when creating interactive or animated analogy visualisations; taking on board multimedia theories, considering the audience's existing knowledge, and avoid overloading the viewer [8, 36].

Conclusion

Animations may not just be useful to communicate known and accepted hypotheses, but could also enable scientists to question and discover why their hypotheses may or may not work. The benefits of using visual analogies to convey complex molecular and cellular data in a more palpable form is an interesting area of research, although it is clearly in need of more effective evaluation methods.

Researchers have access to a great abundance of scientific data, and the best way to visualise this wealth of information remains a challenge. Digital media can reach an increasingly wide audience, and more ideas may be shared this way. Whilst many scientists still use pen and paper to enhance their thought processes and communicate ideas to their peers, animations may one day evolve into a modern-day thinking tool. This could become increasingly popular as computer technology for creating molecular visualisations based on real data continues to become more widespread, accessible and user-friendly.

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Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

Figure Legends

Figure 1

Model assets used in the animation. (A) Keratocyte cell. (B) Actin filament and monomer. (C) Mountain climber (SuperAverageMan ztool). (D) Rock face. (E) Shark tooth (to represent cell adhesions). (F) Gear (to represent myosin II). (G) Tank.

Figure 2

Animating actin polymerisation. (A and C) Actin monomers constrained to individual motion curves and keyframed in Maya. (B) Plan for actin polymerisation at the leading edge and rendered views. (D) Actin pushing *L. monocytogenes* inside the cell.

Figure 3

Animating keratocyte crawling. (A) Cell with the lattice deformer in Maya. (B and C) Top views with lattice vertices adjusted after 30 frames.

Figure 4

Mountain climber model rigged in Zbrush (A) and positioned on the rock face (B). Animating the treads of the tank model in Maya (C and D).

Figure 5

Rendered scenes of the tank analogy cell. (A and B) Whole and cross-sectional cell views. (C and D) Focal adhesions depicted as shark teeth; larger adhesions coloured pink and nascent complexes in red. (E and F) Actin depolymerisation at the rear and myosin motor action (green gear); dissociation of mature focal adhesions (purple).

Figure 6

Scenes from the completed animation. (A) Title screen. (B and C) Introduction to cell locomotion. (D and E) Explanation of the role of actin and polymerisation in cell movement. (F) *L. monocytogenes* experimental data. (G) Mountain climber analogy. (H) Tank analogy.

Supplementary Figures

S1 A: Software and a brief description of their use in the project

Software	Description of use
Maya 2015 (Autodesk) (http://www.autodesk.com/education/free-software/maya)	Modelling and Animation
Molecular Maya (mMaya) (Clarafi) (https://clarafi.com/tools/mmaya)	Free plugin for Autodesk Maya that lets users import, model and animate molecular structures
Zbrush (Pixologic) (https://pixologic.com)	For improved modelling, sculpting and texturing
Adobe Audition CC 2015 (http://www.adobe.com/uk/products/audition.html)	Audio editing and mixing application
Adobe After Effects CC 2015 (http://www.adobe.com/uk/products/aftereffects.html)	Digital visual effects, motion graphics, and compositing application
Adobe Photoshop CC 2015 (http://www.adobe.com/uk/products/photoshop.html)	Raster graphics editor

S1 B: Microscope movies used in the animation

Movie	Cell type	Source
A	Chick heart fibroblasts	(Kadir et al.2011) http://jcs.biologists.org/content/124/15/2642.long
B	Neutrophil	(Alberts et al. 2008) Molecular Biology of the Cell, 5 th addition.
C	Dictyostelium	Insall Lab
D	Mouse skin melanoblasts and keratinocytes	Shereen Kadir (unpublished data)
E	Fish Keratinocyte	https://www.youtube.com/watch?v=RTjYXBnMcgs
F	Mouse skin melanoblasts	Shereen Kadir (unpublished data)
G	Dictyostelium	Insall Lab
H	Fibroblast with <i>L.monocytogenes</i>	(Alberts et al. 2008) Molecular Biology of the Cell, 5 th addition.