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An undergraduate perspective on LINDSAY Composer: bridging the gap between software engineering and physiology

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LINDSAY Composer is a project aiming to capitalise on advances in computer technology, providing a fully immersive and interactive platform for modelling physiological systems. Allowing its users to design models using a set of customisable, shared components, LINDSAY Composer permits for a diverse range of systems to be simulated, as well as allowing for these systems to interact with one another[1]. We present three undergraduate projects here, reflecting on the adaptability of LINDSAY Composer; the program has allowed for novel user-interactions to be implemented, alongside two simulations, the nephron and reflex arc, to be modelled with high accuracy and performance. Despite being disjoint, these projects are all designed within LINDSAY Composer and are built upon the same basic components. Their unique functions and behaviours are implemented as specialised components that confer system-specific behaviours, illustrating the Composer's potential applicability in educational and clinical settings as a platform for providing a straightforward means of visualising any system of the user's choosing, as well as its capacity to adapt to ever-changing technological paradigms.

Introduction

The LINDSAY Virtual Human Project at the University of Calgary is developing a fully interactive, three-dimensional computer model of human anatomy and physiology to be used in medical education. LINDSAY Presenter, one of the key LINDSAY software tools, is used to provide a fully interactive model of human anatomy, while LINDSAY Composer provides another set of tools for the construction of physiological models[1]. LINDSAY Presenter is mainly used to illustrate the structures of human anatomy in three-dimensional space, while LINDSAY Composer provides tools for the construction of physiological simulations and is intended for use in both educational and research-driven settings[1]. Both projects are driven by the common goal of creating an immersive environment for modelling the human body and simulating its physiological functions. The component-based design of the simulation environment in LINDSAY Composer allows it to capture virtually any system within the human body[1]. Moreover, as a project presently still in development, efforts have also been directed at improving the user experience. In this paper, we describe three independent research projects that are unified by their usage of LINDSAY Composer. One of these ventures focused on improving the usability of LINDSAY Composer through the implementation of a novel gesture-based adjunct to the interface using the Microsoft Kinect, while two of the projects

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built upon LINDSAY Composers infrastructure to create physiological simulations and aimed to capture the behaviors of their modelled systems. The first simulation we present models the movement of action potentials through the reflex arc pathway of the nervous system, while the second replicates the inner workings of the nephrons. Because each of these projects were built upon the same components, they share commonalities that allow them to work synchronously with other systems within LINDSAY Composer.

Background

LINDSAY Composer models biological systems in silico, enabling the simulation of 'wet' systems in a 'dry' environment[1]. This approach reduces experimental costs, permitting for experiments that would otherwise be unfeasible in the wet lab setting. While in silico models are well-established in the biological sciences, their creation requires extensive expertise in computer science[2]. Computer models share similarities in that all models are abstractions of a real-world system, representing entities of interest. All models are run to approximate expected behaviours, assuming a set of conditions hold true. However, much duplicated effort results from the fact that few simulations build upon the technical efforts of preceding simulations. LINDSAY Composer aims to ameliorate this by providing a set of essential capabilities, along with the tools required to customise and extend simulation behaviour depending on the user specifications. The LINDSAY Composer uses the agent-based approach towards modelling, where autonomous entities, known as agents, interact with one another and the simulation environment, giving rise to complex behaviours[2,3]. Biological systems share parallels with the agent-based approach in that they consist of functional units (agents). As such, the agent-based approach is an intuitive means of conceptualising a physiology simulation. This reduces the need for using mathematical models in the simulation: while powerful, such models are designed to simulate specific situations and have little applicability in other scenarios[4]. Within the LINDSAY Composer, the agents are organised into a hierarchy of entities, called components, that possess state and behaviour attributes[1]. These traits allow the agents to interact with one another and with the simulation environment in a myriad of ways.

Developing a Natural User Interface Using the Microsoft Kinect

Substantial effort is spent exploring novel technologies, a key element within the LINDSAY Virtual Human. One such effort involved creating a natural user interface (NUI), permitting a user to control LINDSAY Composer by performing gestures with her body rather than directly manipulating a physical input device. NUIs reduce the number of abstractions separating the user from the application: while traditional input models have the user manipulate a physical device, NUIs eliminate this intermediary device, instead mapping the user's movements directly to changes in the software system[5]. This shift makes the LINDSAY suite more accessible for novice users, while also providing an efficient means of control for seasoned users. In the LINDSAY project, the developed NUI enables intuitive navigation through three-dimensional physiological simulations, granting the opportunity to observe and control real-time processes using only body movements. Released in 2010, the Microsoft Kinect is a platform that allows NUI interactions. Originally released for the video games market, it has become the first widely deployed NUI device: enthusiast developers would subsequently design custom tools to extend the Kinect's capacities[6]. The OpenNI library is one such tool and was used to generate user positioning data, including the three-dimensional locations of the user's head, elbows, hands, and other skeletal points[7]. Abstractions such as gesture recognition were then built atop this data for usage within LINDSAY Composer. The initial NUI support in LINDSAY is not meant to replicate all interactions possible with traditional input devices such as the mouse and keyboard; traditional devices have had thirty years of history and evolved a rich interaction language amongst both users and developers[13]. By comparison, NUIs are still immature and thus, not widely used, precluding their ability to replace traditional methods. Presently, the NUI in LINDSAY permits control of functions useful in presentation settings, allowing the user to manipulate LINDSAY simulations using only gestures. Specifically, this NUI system presents three primary functions:

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head tracking, camera manipulation, and object manipulation. The LINDSAY NUI's head-tracking functionality captures the position of the user's head in three-dimensional space and manipulates the user's view accordingly to create the illusion that the user's screen is a window into the virtual world, rather than merely a two-dimensional projection of it (Fig. 1). If the user leans left, her view shifts to reveal content on the right side of the screen previously hidden, much as though she were standing at a storefronts window and leaned to look at an obscured object.

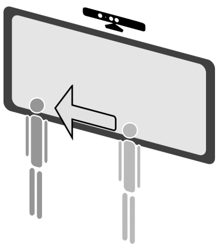

Figure 1:
By tracking the position of the users head in three dimensions and altering the users view accordingly, the interface promotes the illusion that the screen is simply a window into the virtual world, rather than a rendered projection of it.

Aside from head-tracking, OpenNI provides two additional means for manipulating elements in the virtual world. Camera manipulation is the first of these means and enables gesture-based navigation of three-dimensional space (Fig. 2). Navigating three spatial dimensions with a mouse and keyboard is challenging, as the physical mouse can move only across the two-dimensional surface of the user's desk, but must permit navigation through three-dimensional virtual space[9]. Usage of the Kinect in LINDSAY removes this constraint, allowing direct virtual movement via three-dimensional gestures in the physical world. If the user pushes her right hand forward or backward, up or down, or left or right, her viewpoint within the virtual world moves accordingly. Beyond position, the user may also control orientation, moving her left hand to look in a direction of their choosing.

Object manipulation is the last of the NUI functions within LINDSAY Composer. Moving objects within three-dimensional space shares the same challenges encountered in camera manipulation and is similarly simplified by the use of NUIs. Within

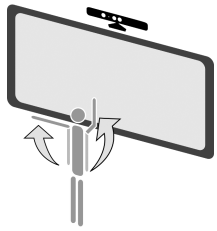

Figure 2:
Camera manipulation is performed by the user moving her right hand forward or backward, up or down, or left or right. Likewise, she controls her orientation by moving her left hand in the desired direction. In this manner, the task of navigating three virtual dimensions—quite challenging with a mouse that can move only on a two-dimensional surface—is made more intuitive.

LINDSAY Composer, the user's right hand controls an on-screen cursor that may be used to pick up objects of interest (Fig. 3). However, this gesture is constrained by the Kinect sensors limited resolution, which precludes reliable discrimination of discrete finger positions, necessitating that a two-handed gesture be used. This illustrates how NUI systems are presently restricted by the incipient state of their supporting technology: improvements will permit more natural gestures, such as a more natural grabbing motion to move objects as they would in the physical world.

Great potential exists to expand the NUI capabilities in LINDSAY Composer. Rapid advances are occurring in NUIs' underlying technology, with post-Kinect devices offering sufficient resolution to distinguish the user's fingers from her hand, permitting finger-based gestures[10]. Simultaneously, as NUIs become commonplace, gesture idioms will develop just as they have with the mouse and keyboard, permitting richer and more intuitive interactions[11]. With device abilities and gesture conventions progressing in lockstep, NUIs will grow pervasive over the coming decades.

A Reflex Arc Simulation

The reflex arc model is one of the exemplary models for the potential of future simulations within LINDSAY Composer. The current version of the reflex arc model has been achieved using a combination of several methods available through

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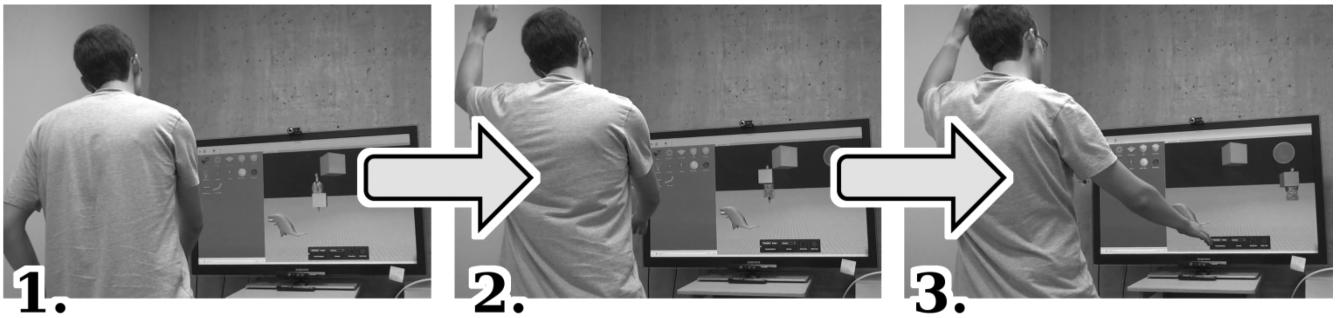

Figure 3:
Objects within the virtual environment are moved via a three-step process. 1. The user positions the cursor over an object of interest using his right hand. 2. The user raises his left hand above his shoulder to pick up the object. 3. The object follows the user's right hand until he lowers his left hand below his shoulder.

the help of the LINDSAY team. The capacity to design simulations from common components presents a substantial advantage: allowing for specific components to be chosen for the task at hand. This allows for models to be more dynamic and flexible, contrasting the more constrained approaches that traditional models take. The reflex arc is an ideal model, owing to its simplicity relative to other important bodily functions, such as the quantity of participating components and the systems interactions with other systems. Reflex arcs in the human body do not require conscious decisions from the brain, making them vital processes that help to protect the body from any immediate harm (e.g. extreme temperatures or a sharp object damaging epidermal tissue)[12]. Since the brain receives a signal only after the body has responded on reflex, the simulation should not be unfeasibly complex. The model of the reflex arc utilizes high-quality 3D objects created in Autodesk MAYA specifically for the simulation[13,14]. Currently, it is composed of skin cells, a stimulus, the sensory, motor, and interneuron neurons and muscle cells. The neurons are all composed of a cell body, nucleus, axon, Schwann cells, axon terminal, and dendrites (Fig. 4).

As the propagation of the electrical signal is the basis for the reflex arc model, important ions such as sodium, potassium and chlorine are also present at every node of Ranvier, the unmyelinated axon between Schwann cells (Fig. 5), and the axon[20]. These ions, along with the axons, dendrites, muscle cells and stimulus are key agents: interactions between them are vital for an accurate representation. Most of the simulation is driven by electrical potential, a value that is continually measured by calculating the proportionally representative numbers of ions at several points of the neuron chain. When the stimulus strikes the nociceptors of the sensory neuron located at the skin cells, the force of the strike is translated into an electrical signal. A sufficiently strong signal triggers a propagation signal beginning at the closest node of Ranvier[15].

Since the signal acts by increasing the voltage at the subsequent node, it causes voltage-dependant channels to open and let ions through. This is shown instead by giving ions a pre-determined probability of flowing in/out of the node or bouncing against the membrane, using a few differential equations based on published data on voltage channels to regularly change the probability according to the current voltage. A real-time voltage graph is generated by the simulation and illustrates that, although variations are seen as they would in vivo, the action potential curve of the reflex arc model is still able to closely resemble the theoretical curve in everything but the time scale (Fig. 6). The signal is then illustrated as propagating through the axon of the sensory neurons, jumps to the interneuron in the dorsal horn, follows a similar process to reach and propagate to the motor neuron, and finally reach the muscle cells. The interneuron evaluated the pain response before it continued propagating, so the muscle cells receive instructions on how to react to the stimulus, and react accordingly.

While the reflex arc model is reasonably accurate, additional refinement is necessary before this model is ready for any research or educational purposes. Future additions will incorporate the ability to modify

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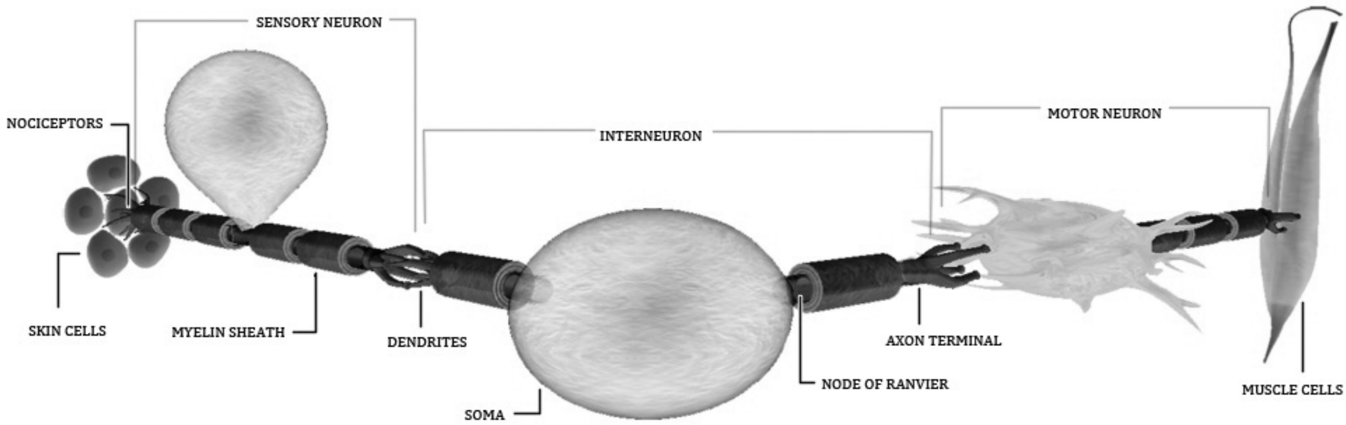

Figure 4:
The full layout of the reflex arc simulation, beginning at the skin cells, and ending at the muscle cells. All components are fully interactive, 3D structures built into LINDSAY Composer.

Figure 5:
A close-up of a section in Figure 4. Potassium, Sodium and Chlorine ions are seen inside and around the Nodes of Ranvier.

important parameters that will change the signal propagation, as well as the ability to show the effects of external factors on signal propagation. The inclusion of these factors will lead to an increasingly accurate model of the pain reflex arc that will be an asset for both the classroom and research lab.

The Virtual Nephron Model in LINDSAY

In the human body, blood filtration and homeostasis are handled by the renal system[17]. The renal system consists of the kidneys, as well as the structures responsible for moving urine out of the body. The kidneys are composed of hundreds of thousands of nephrons, compact structures responsible for the filtration of wastes from the bloodstream and reabsorption of vital compounds[17]. As the nephrons play a critical role in maintaining homeostasis, they serve as the fundamental unit of filtration in the kidney: defects in the nephron may result in renal disease. Thus, effective understanding of these low-level mechanisms is essential towards understanding renal diseases and any potential targets for treatments[18]. However, difficulties arise in studying nephrons in vivo: such a procedure would be highly intrusive and cannot be done on human patients. The utilization of in silico methods, such as the LINDSAY Virtual Human, has offered the means to overcome this particular limitation, allowing for these processes to be observed in an interactive computational model. As the unit of filtration, the nephron is an ideal structure to model, given that it carries out all the kidneys essential functions and thus can be viewed as an independent unit (Fig. 7). These units are represented as the agents and carry out two essential processes: flow and filtration. In order to prepare such a model, several entities must be added to the simulation space. These entities have different physical properties, allowing them to carry out different functions within the model. In both cases, a hollow vessel is present, and entities flowing within them are constrained to the volume of the vessel. Additional components are then added along the vessel to confer flow and filtration behaviours.

Flow was the first aspect to be implemented: the mechanism behind the fluid flow component allows entities to flow smoothly within vessels. This component assigns a ray-casting mechanism to each entity (Fig. 8); the ray can be thought of as a line

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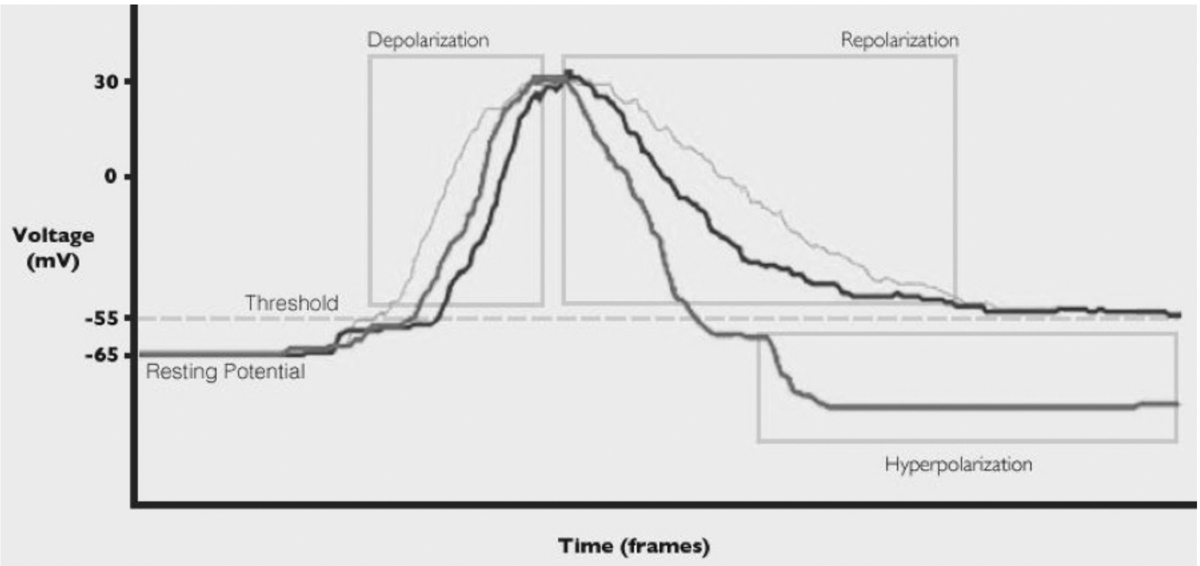

Figure 6:
A graph showing the change in voltage in the first Node of Ranvier of three real-time reflex arc iterations. These curves follow a similar pattern to the theoretical and experimental voltage graphs of the giant squid axon. [17]

projected a fixed distance in front of the entity in computer graphics[19]. If the ray intersects with a surface, the underlying code determines the distance between the surface and the entity, and applies a force to steer the entity smoothly along the vessel walls without collisions. The generic implementation of this solution allows for use of the same algorithm in other flow simulations.

Within the nephron, filtration is accomplished by either diffusion or transport. Diffusion is achieved by a molecule moving down a gradient across a membrane, and transport is carried out with the assistance of specialised protein channels. In both cases, a particular substrate must move across the nephron membrane into the interstitial space and across another membrane into an adjacent capillary, without allowing the movement of other substrates[20,21]. In the nephron model, water reabsorption was implemented in the descending loop of Henle, a region of the nephron that is impermeable to ions[21]. Within the LINDSAY Composer, the nephron is represented as a single entity impermeable to all substrates within the nephron lumen. Permeability is controlled by collision attributes, which determine whether an object can collide with another[22]. To allow water molecules to move between the nephron and the intertubular capillaries, a channel was implemented to recognise

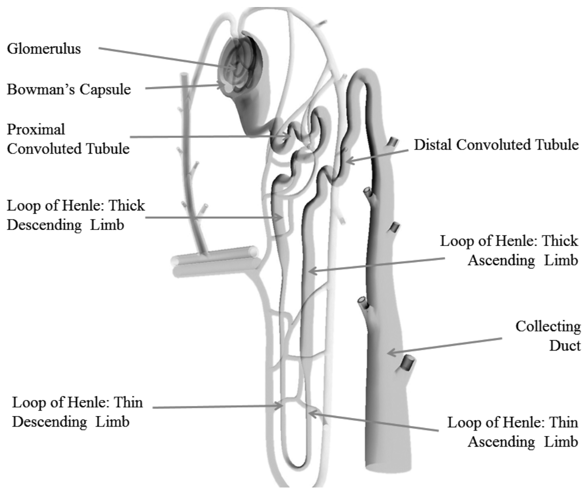

Figure 7:
Structural components of the nephron in LINDSAY Composer. Solutes dissolved in the blood filter through into the Bowmans capsule and travel through the nephron lumen. Depending on the solute type and body conditions, the solutes are either secreted at the collecting duct or else reabsorbed into the body.

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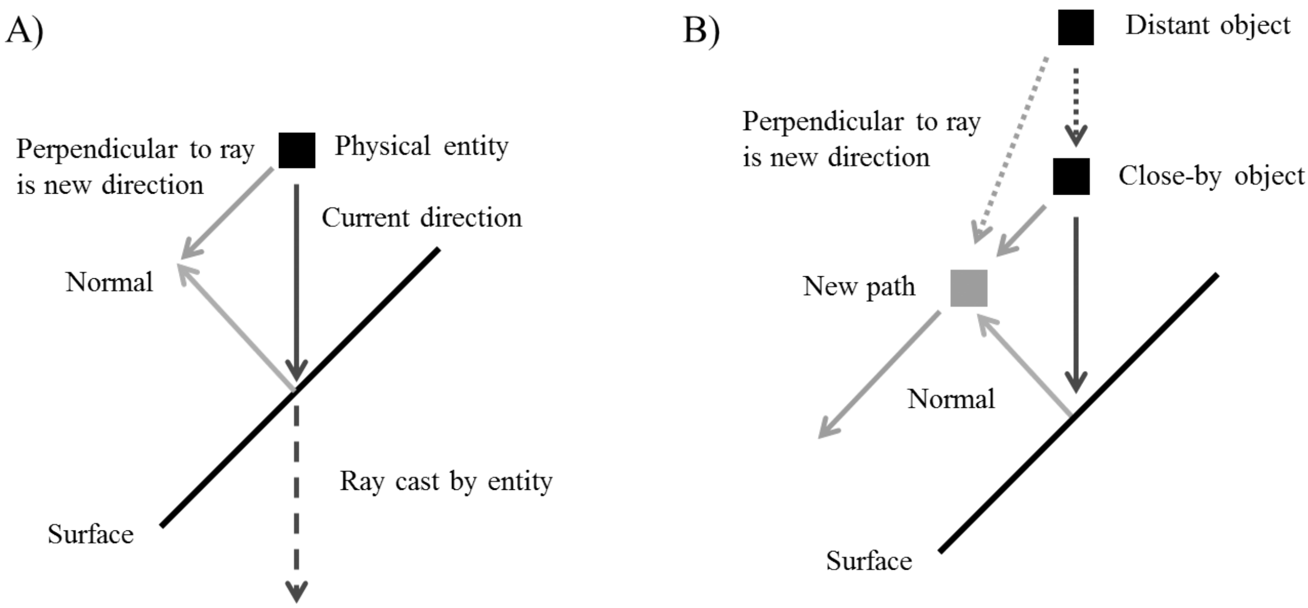

Figure 8:
Ray casting mechanism. All entities in within the flow fields cast rays that detect surfaces in front of it (A). Depending on its distance, a force is applied to push the object along the vessel wall rather than into it. The magnitude of the force is inversely proportional to the entitys distance to the wall (B).

and alter the collision properties of the water molecules, allowing them to pass through the nephron walls (Fig. 9). Once the molecule enters the capillary, the channel resets the molecule's collision properties, and it resumes flowing through the vessel. Based on the rate of flow, the transporters can shut down and prevent the reabsorption of water, mimicking regulatory elements such as vasopressin, which alters membrane permeability based on water levels[23]. The channel is configured to detect and modify only water molecules, so sodium molecules in the lumen remain unaffected. These behaviours function synchronously to model filtration, allowing water molecules to move into the adjacent capillary while sodium ions flow by undisturbed.

Together, flow and filtration are the two essential aspects that produce a simple, highly visual model of the nephron (Fig. 10). Used in an educational context, this model can portray processes that are otherwise not practically presented through more traditional media. The functionality of the model, coupled with the inherent interactivity of the LINDSAY Composer, represent the increasing viability of virtual instruction in physiology.

Conclusion

The diversity of the three projects presented reflects the adaptability of LINDSAY Composer. Through its usage of a single, streamlined system for designing simulations, LINDSAY Composer presents a platform that permits a diverse range of models and features to be built from a small set of basic components, in turn making it possible to build new simulations from existing ones. Whereas the Kinect-based project focused on improving the softwares usability, the biological projects aimed to design encapsulated simulation agents. Taken together, these aims will forge the LINDSAY Composer into a powerful, user-friendly platform for modelling physiological processes that will find applicability in education and research settings.

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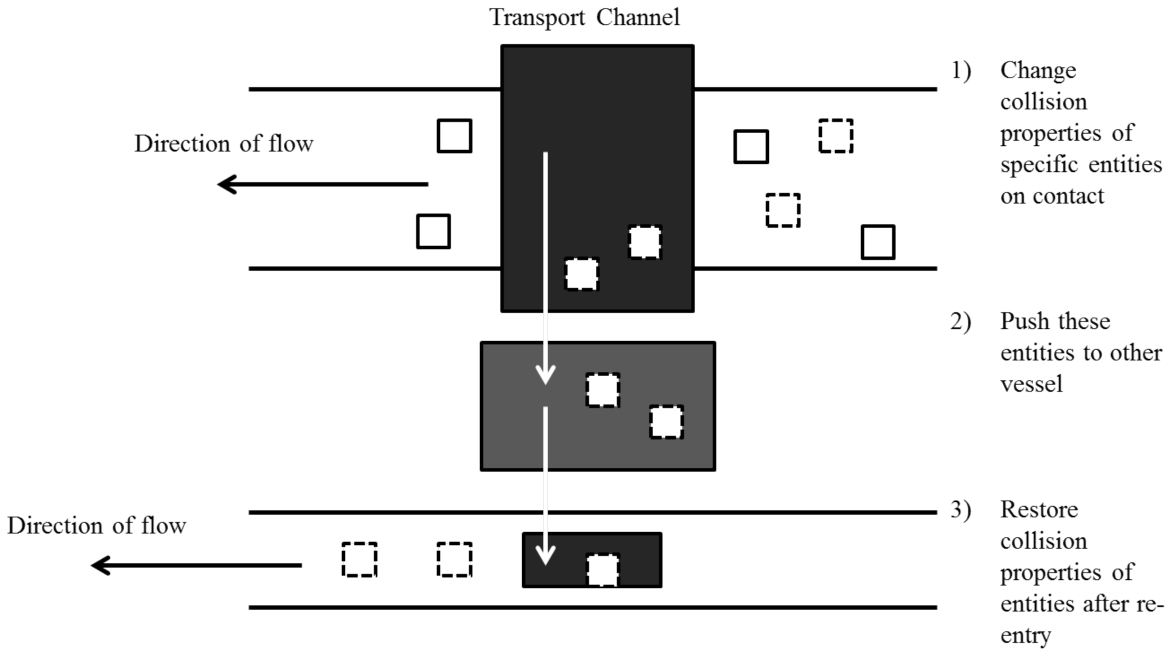

Figure 9:
Schematic of filtration mechanisms. Objects in a vessel are impermeable and cannot escape. The transporter in LINDSAY Composer is capable of detecting specific objects (dashed squares), modifying them to pass through the vessel walls and pushing them into an adjacent vessel. Their properties are restored once they enter the vessel, and they continue to flow normally.

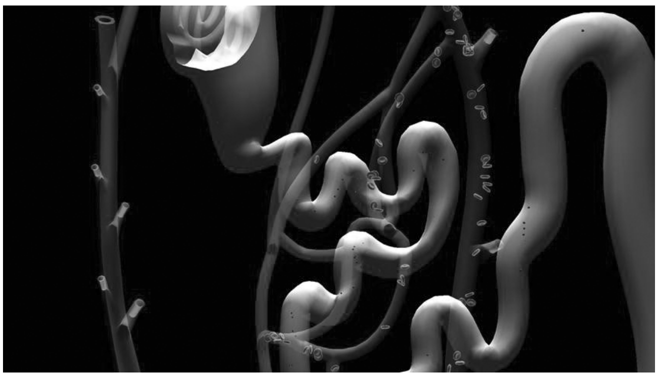

Figure 10:
The Virtual Nephron in LINDSAY Composer. Blood cells flow through the blood vessels outside of the capillaries, while water and sodium ions flow through the nephron lumen. The specificity of the channels allows only water to be reabsorbed into the capillaries from the nephron lumen.

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