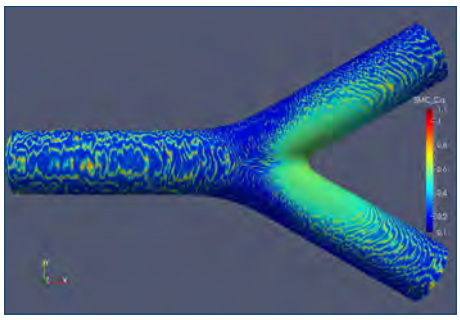
# In silico experiments on human bodies

**New Zealand is a world leader in mathematical modelling of some human body processes, enabled by our burgeoning knowledge of cell biology.**

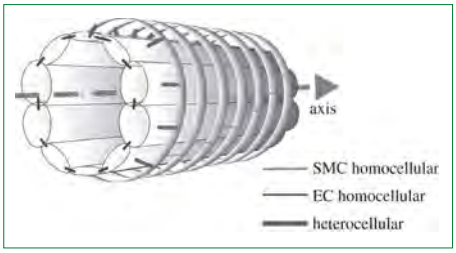
Professor Tim David, right, Director of the University of Canterbury High Performance Computing Centre, is modelling how the cells in the walls of our arteries and in our brains communicate and become dysfunctional.



Waves of calcium ions move through an arterial bifurcation, similar to the carotid artery.

Atherosclerotic plaques are growths from the artery wall, up to five cm long, which can eventually block arteries, starving heart cells of oxygen and causing a heart attack. "Somehow thousands of cells communicate to make plaques grow, and only where the arteries split," Tim says.

"Arteries are made of two cell types - endothelial cells (ECs) that line the inside of the artery, and smooth muscle cells (SMCs) that wrap around the outside wall of the artery and allow it to contract or dilate," he says. "They are linked with gap junctions, proteins forming a tunnel that allows ions such as calcium or chloride and small molecules to pass from one cell to another."




A straight artery segment with long endothelial cells coupled to surrounding smooth muscle cells.

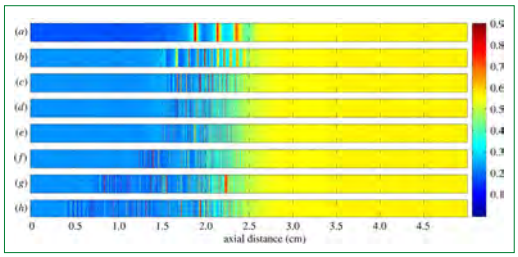
Right: The complex pathways for calcium ($Ca^+$) and potassium ($K^+$) ions and inositol trisphosphate ($IP_3$) cell messenger molecules in the endothelial and smooth muscle cells that make up most of the vessel wall. $IP_3$ molecules help increase calcium concentration in cells.

"We can form mathematical equations representing the conservation of ions in a cell. If you ignore spatial variation, you have a time-dependent ordinary differential equation (ODE) for each of the many ions in a cell. Mathematically, ion transfer between cells is all non-linear." His team has modelled these ODEs for millions of cells in the wall of an artery, and coupled them with ions diffusing through the gap junctions between cells, and blood flowing through the space inside the artery. The model includes the oscillation of ion concentrations in smooth muscle cells under certain conditions, defined by geometry and linked endothelial cells. The model links cellular chemistry, the geometry of the arterial join and the fluid dynamics of blood, and aims to simulate the early development of heart problems, before they can be detected by diagnostic methods.

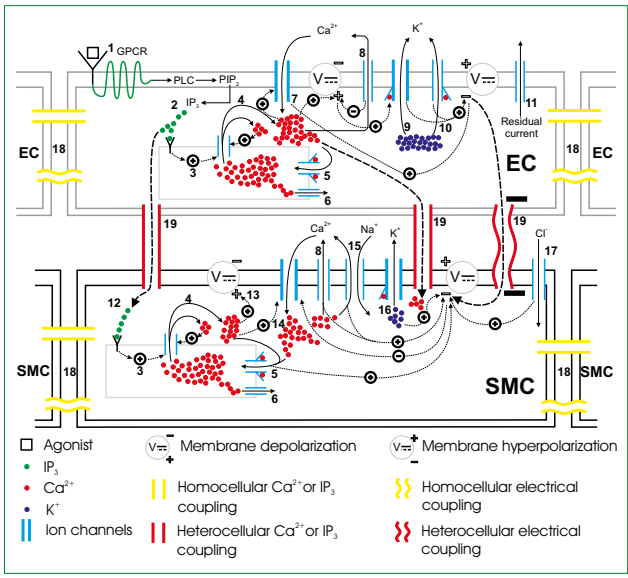
"All this creates millions of time-dependent, coupled, non-linear, ODEs" - the computerised equivalent of a huge flock of birds or a massive, fast-moving tight school of fish. This type of co-ordinated movement is called emergent behaviour. An ordinary desktop computer with four processors can't run the code for these ODEs – "it requires thousands of processors, because we can store only a small number of ODEs in the memory of one processor," says Tim.

Simulations on the IBM BlueGene/P supercomputer at the University of Canterbury, which has 8,192 processors, "suggest that the emergent behaviour in arteries is a series of complex waves of calcium ions moving through the arterial wall; they create fantastic spatial patterns," he says.

Tim's team has already validated their model in a single cell. The usual way to test a multicellular model is in animals, but "in silico models can do things that would be impossible in the lab with a poor little animal".




The concentration of calcium ions in smooth muscle cells in time steps between 2m to 2.75h for an artery with a 50μm radius, ranging from high (red) to low (dark blue). Ions did not oscillate for the first 30 minutes (a-e), but after an hour (f-h) they spread to upstream cells.




### The Goldilocks brain

The other area Tim David's team is modelling is the regulation of blood flow, oxygen and glucose in the brain. "The brain is like Goldilocks - it swells if there's too much blood and faints if there's too little. So it automatically regulates the supply; when we stand up or sit down, the vessels contract or dilate to allow the right amount. Certain parts of the brain need more oxygen and glucose when we read, or listen or think."

"Neuro-vascular coupling (NVC) units in the brain start with a neuron, close to the head of a star-shaped astrocyte, whilst the foot of the astrocyte is close to a smooth muscle cell." Like arterial cells, these cells communicate with ion transfers. Tim's team has built a complex model of a NVC unit and linked it with millions of others and with blood vessel cells.

"We're beginning to understand how NVC units work normally and we can experiment in silico to see what happens when certain parts become dysfunctional. We believe there is a strong relationship between the way the brain regulates blood and Alzheimer's disease."

The code Tim's team has tested on BlueGene has enabled them to win time on the fifth largest supercomputer in the world, the BlueGene/Q in Chicago, which has 786,432 processors. They apply each year and will know this winter whether this year's application has been successful. Their allocation in the last two years of two million core hours enabled them to use, say, 400,000 processors for five hours. "To solve 100 million cells in a single coronary artery, we need that number of processors," says Tim.

## PROOFS AND PRIZES

### ABEL PRIZE 2016

Sir Andrew Wiles, who in 1994 proved Fermat's Last Theorem (that no three positive integers $a$, $b$, and $c$ satisfy the equation $a^n + b^n = c^n$ for any integer value of $n$ strictly greater than two), has been awarded the Abel Prize for 2016 by the Norwegian Academy of Science and Letters, worth about €750,000 Euro.

**See:** www.abelprize.no

### SOLUTIONS TO SPHERE-PACKING PROBLEMS

Maryna Viazovska, left, a Ukrainian postdoctoral researcher in Berlin, has proved a significant generalisation of the centuries-old Kepler Conjecture, about the most efficient sphere-packings in three dimensions. The problem was originally solved by Thomas Hales about 18 years ago, using computer analysis of a large number of cases.

In March 2016, Maryna showed that the $E_8$ packing gives the best sphere packing in eight dimensions, and that the Leech lattice gives the best packing in 24 dimensions.

Maryna's remarkable proof for $E_8$ takes only 23 pages, using modular forms. She found the elusive auxiliary functions for $E_8$ and the Leech lattice that led to her proof. These functions appear in most number theory proofs, and may take the value zero for for many arguments.

**See:** www.plus.maths.org/content/packing-balls-higher-dimensions or www.quantamagazine.org/20160330-sphere-packing-solved-in-higher-dimensions

*Photo: Petra Lein, 2013. CC BY-SA 2.0 de*

## MATHEMATICAL EVENTS

4-8 July 2016, Wellington **Mathematics in Industry NZ Study Group** See www.minz.org.nz

8-14 August 2016, across NZ **Maths Week** See www.mathsweek.org.nz

27-30 November, Auckland **Joint Conference of the NZ Statistical Assn and Operations Research Society of NZ** See www.stats.org.nz or orsnz.org.nz/conf50

4-8 December 2016, Wellington **NZ Mathematics Colloquium**, including a **Maths Education Day** on 8 December Email peter.donelan@vuw.ac.nz

14-18 August 2017, Oaxaca, Mexico **3rd Congress of the Pacific Rim Mathematical Assn** See www.primath.org/congress/prima-2017

# Models for breathing

Alona Ben-Tal, of Massey University at Albany, studies how breathing is regulated in humans and birds. Breathing alters levels of oxygen and carbon dioxide in our blood: "We know that if we run out of oxygen, our bodies can increase how deeply and often we breathe to bring in more air. If carbon dioxide levels are low, we reduce breathing."

"We can breathe quickly and shallowly or deeply and slowly and get the same change in blood gas levels," she says. "Different people do it differently and we don't know why our systems go one way or the other. I'm trying to answer that question."

To develop mathematical models, "you need a good understanding of how the system works, so you talk to physiologists and read their papers until you come up with a schematic model. You then use physical and chemical principles to write the mathematical equations. Once the equations are written you forget the physiology and biology and dive completely into the numerical world, using mathematical principles to solve the model. Then you test it with real-world data and make predictions about things you couldn't measure." One of the mathematical models she developed suggested that sleep apnoea, where breathing regularly and briefly stops, could be created by two different brain mechanisms.

Alona is also interested in the interactions between the heart and the lungs. The human heart, especially in young, fit people, speeds up when we breathe in as muscles around the lung contract, and slows down when we breathe out and the muscles relax. This is called respiratory sinus arrhythmia (RSA). Losing RSA has been linked to heart disease; however, we don't fully understand why RSA helps us.

When Alona used her model to study the interaction of breathing and heart rate she initially thought that increasing our heart rate when breathing in would improve gas exchange in the lungs as research had suggested. "But the modelling didn't support that hypothesis, and we realised something else was going on. We think RSA helps the heart do less work, while keeping blood gases at the right levels."

"This hypothesis has led to some exciting opportunities for treatment," she says. It is being tested in animals by changing the way pacemakers pace the heart with breathing, to see whether it improves heart condition. Alona found the modelling of lung function in birds "fascinating for several reasons. We know that birds cope better than mammals at high altitude, whereas people get Cheyne-Stokes respiration, a form of sleep apnoea".

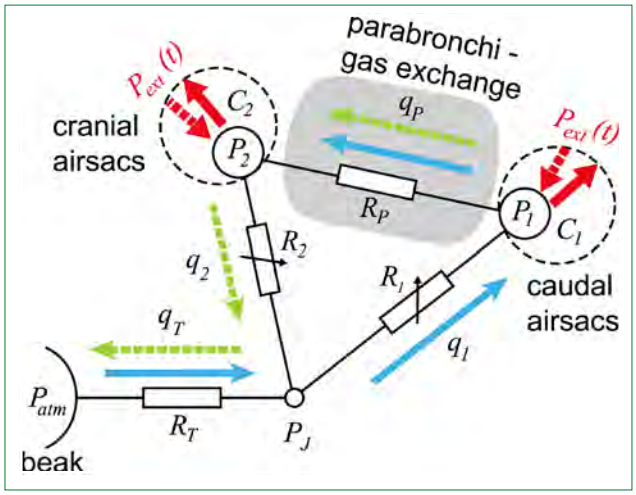
In birds, air flows in both directions through the beak but only in one direction through rigid tubes where gas is exchanged. "It's not clear how it flows only in one direction, as we can't see any active valves in birds' lungs as we can in the heart."

With Emily Harvey, Alona built a simple model of unidirectional air flow applicable for a wide range of parameters and hence to all birds. "There were two surprises – birds can change how fast air flows through their lungs by changing the contraction of the respiratory muscles, which we didn't know."

"The second surprise was that, although we applied sinusoidal forcing to the model to create equal times for breathing in and out, for certain parameter values the breathing-in time was shorter than breathing-out." This is similar to lifting a string (with some nonlinear properties) that is tied to a weight regularly up and down and finding that the weight spends more time up than down, she says.

Alona has recently developed a numerical method based on an 'equation free' approach to help simplify a model of the complex neural system that controls our breathing; "we need models that are easier to simulate and analyse, and this has led to the development of a new mathematical technique" she says.

Alona finds biological modelling fascinating: "You learn new information about biology on one hand, and on the other hand you get interesting mathematics from biological applications. And maths can help translate results from the lab to people."




**Left: A schematic model of one side of a bird's respiratory system**
$P_1$ and $P_2$ represent the pressure in the two airsacs; $C_1$ and $C_2$ their compliance. The pressure outside the airsacs, $P_{ext}(t)$, varies as respiratory muscles make the sacs inflate and deflate. $P_{atm}$ is atmospheric pressure. There is resistance to flow, $R$, and airflow, $q$, between each part of the system. Blue arrows represent air flow in, and green arrows the flow out. *Taken from Harvey EP and Ben-Tal A. (2016) Robust unidirectional airflow through avian lungs: new insights from a piecewise linear mathematical model. PLOS Computational Biology.*

$$\frac{dP_1}{dt} = \frac{-R_p R_2 (P_1 - P_{atm}) - (R_p R_T + \bar{R})(P_1 - P_2)}{C_1 \bar{R} R_p} + \frac{dP_{ext}}{dt}$$