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Project Title

Validation of a computational model of urinary bladder electrical activity in health and during overactivity

Institutions involved

- Indian Institute of Technology Bombay (R. Manchanda)
- University of Birmingham (K.L. Brain)

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Project Objectives

Technical backdrop/ larger goals

Building computational models of electrical activity in urinary bladder smooth muscle.

Specific objectives

Principally, student and faculty exchange to facilitate technical aspects of project

- 4 PhD students from IIT-Bombay to visit University of Birmingham
- 3 faculty visits [two from UK to India, one from India to UK]

Student visits

- to receive training in electrophysiological methods
- to use this training to gain key experimental data suitable for the development or back-testing of their computational models
- to gain a wider experience of biological research through secondments to other laboratories in the School of Clinical and Experimental Medicine ("taster sessions").

** Students: Shailesh Appukuttan, Chitaranjan Mahapatra, Mithun and Rashmi Sharma.

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Progress & Outcomes

Project started: May 2012

[1-1/4 yrs into 3-year project]

Activities so far

<u>Aug-Sept 2012</u>

- Two Ph.D. students from IIT-Bombay visited University of Birmingham for two months (mid-Aug 2012 to mid-Oct 2012)

<u>Aug-Sept 2013</u>

- The two other Ph.D. students have gone across this year (Aug 2013 to October 2013)

<u>Summary so far</u>

- All student visits completed as proposed

<u>To come</u> [Aug 2013-May 2015]

- Faculty visits: later this year/ mid next year

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Benefits of student trips

- Educated the students about the intricacies, and limitations of experimental research – a critical insight for computational investigators
- Enhanced their ability to interpret experimental protocols and data
- First hand experience of conducting electrophysiology experiments and contraction assays
- Experimental data, so obtained, contributes towards their research thesis and also possibly translate into journal publications
- Tested electrophysiology techniques employed in other domains for smooth muscle research – e.g. Multi-Electrode Array (MEA) recordings which are commonly done on brain slices
- Opportunity to interact with experts and peers in the same and related domains

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Project Outreach

No. of exchanges under the project (including academic staff and students)	4 students [Yet to visit: 3 faculty]
No. of joint publications / research papers	One conference paper + one abstract
Workshops organised (please include details like no of participants/key people/Key speakers and way forward from the workshop)	Not proposed

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Future activities planned

- Success indicator of the project/aspects of the project that you want to disseminate to a wider audience

  * Feasibility of modelling a 3-D syncytium in the NEURON environment

  * Explanation of electrical activity of the detrusor muscle

- Sustainability of the project after the UKIERI funding finishes

  Eminently sustainable. (A) Considerable work will remain to be done on urinary bladder. (B) Extension to other smooth muscles

- Issues and concerns

  Long delay was incurred between project approval arrival of grant, owing to negotiations between IITB and BC. Issues: exact form the MOU ought to take, especially over (a) IP matters (b) legal provisions applying to Indian students and faculty visiting the UK

- Best practices for working on joint bilateral projects

  MOU can be made more amenable to Indian institutions so as to obviate any such delays in future. Details of the transactions available with IITB & BC.

Technical details

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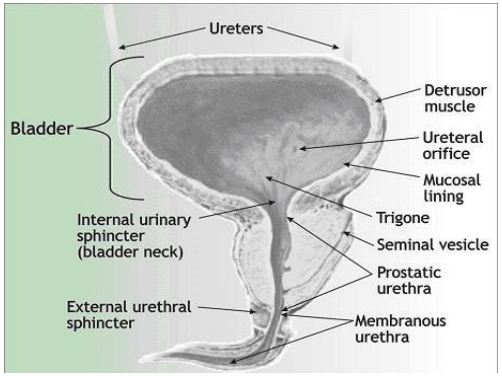
What Do We Wish to Do?

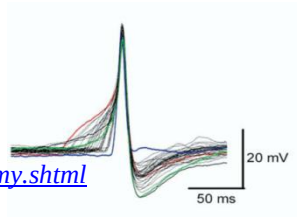
Urinary Bladder:

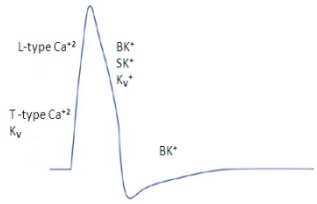
- Work out how it works [esp electrically]
- Make hypotheses about > normal functioning > disorders



http://www.life-tech.com/uro/urolib/urinary_anatomy.shtml

Hayase et al, 2009

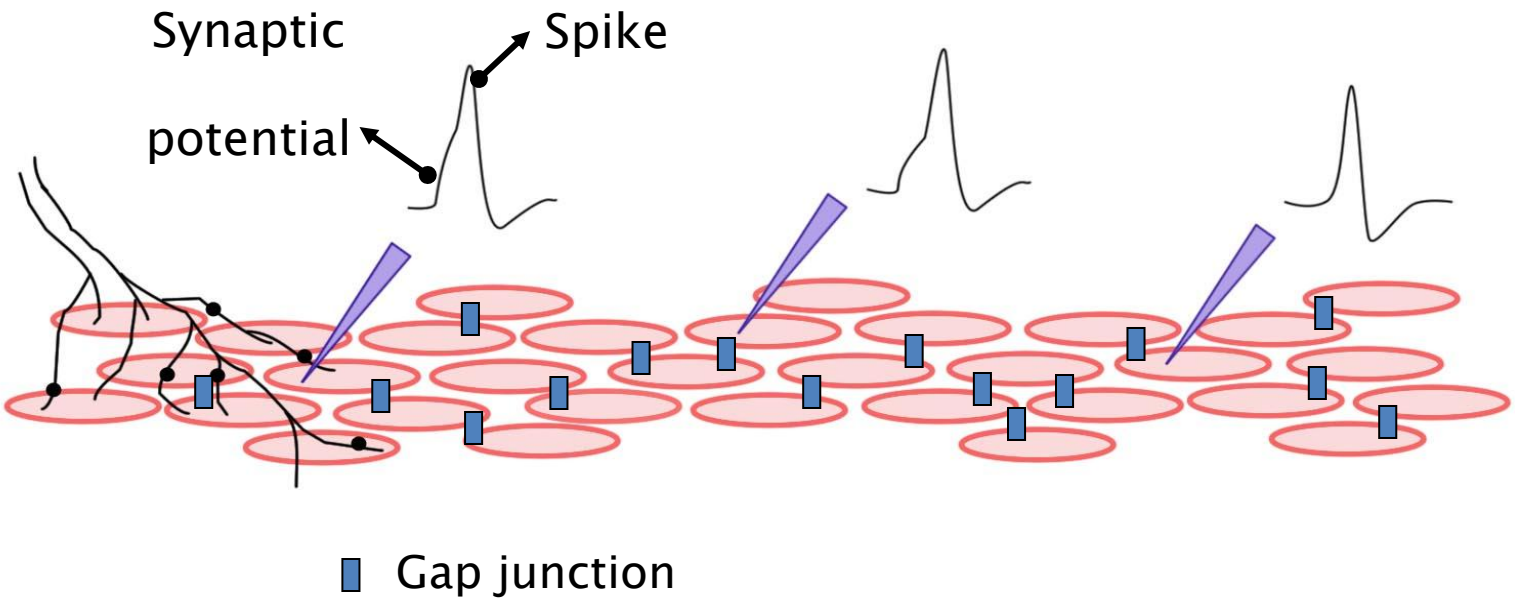




Tasks:

- Analyse signals
- Model them

Microphysiology of smooth muscles



Modelling challenge: using the compartmental modelling approach to model a 3-D syncytium

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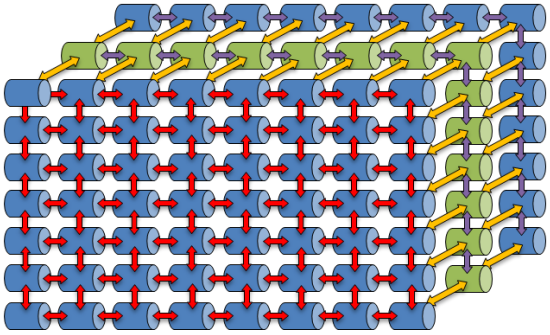
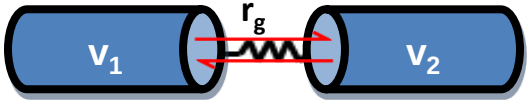
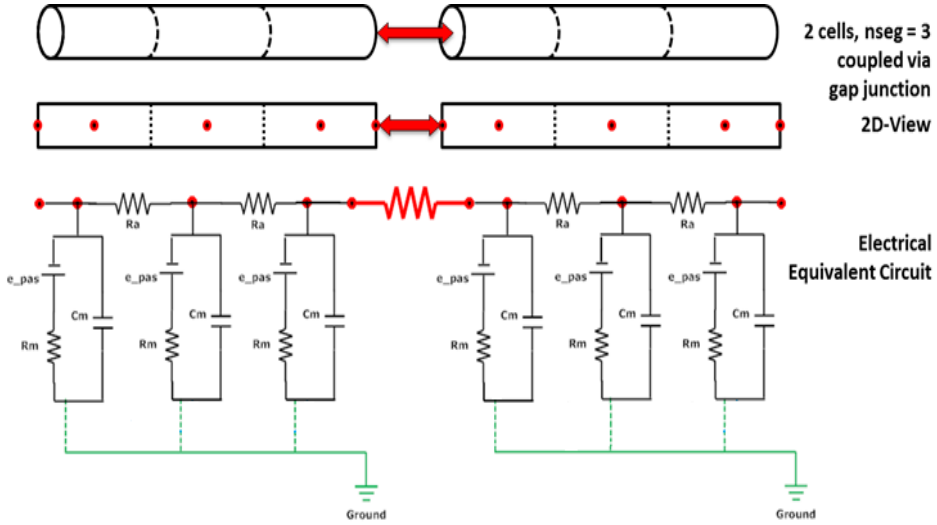
Realizing a 3D Syncytium in NEURON

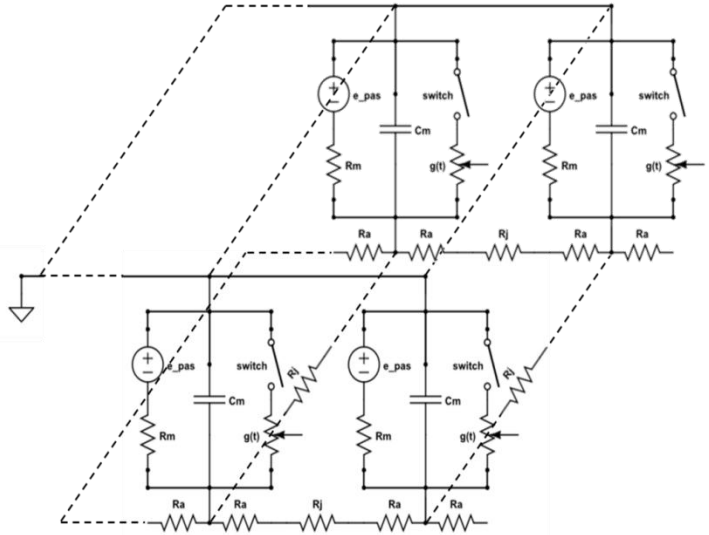


Every Cell
Coupled to 6
other Cells



$$i = (v_1 - v_2) / r_g$$





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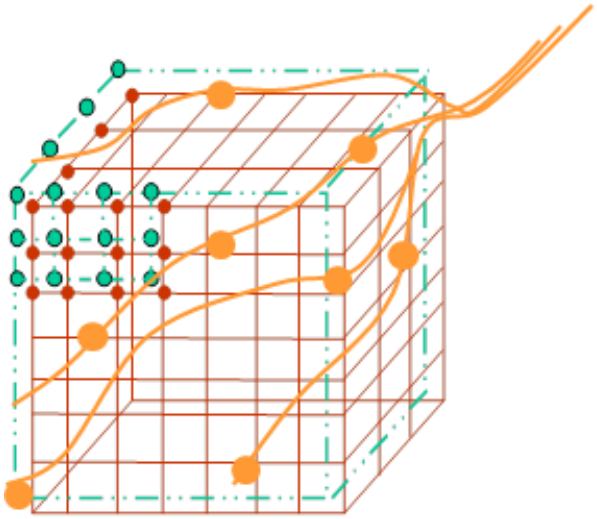
Model Parameters

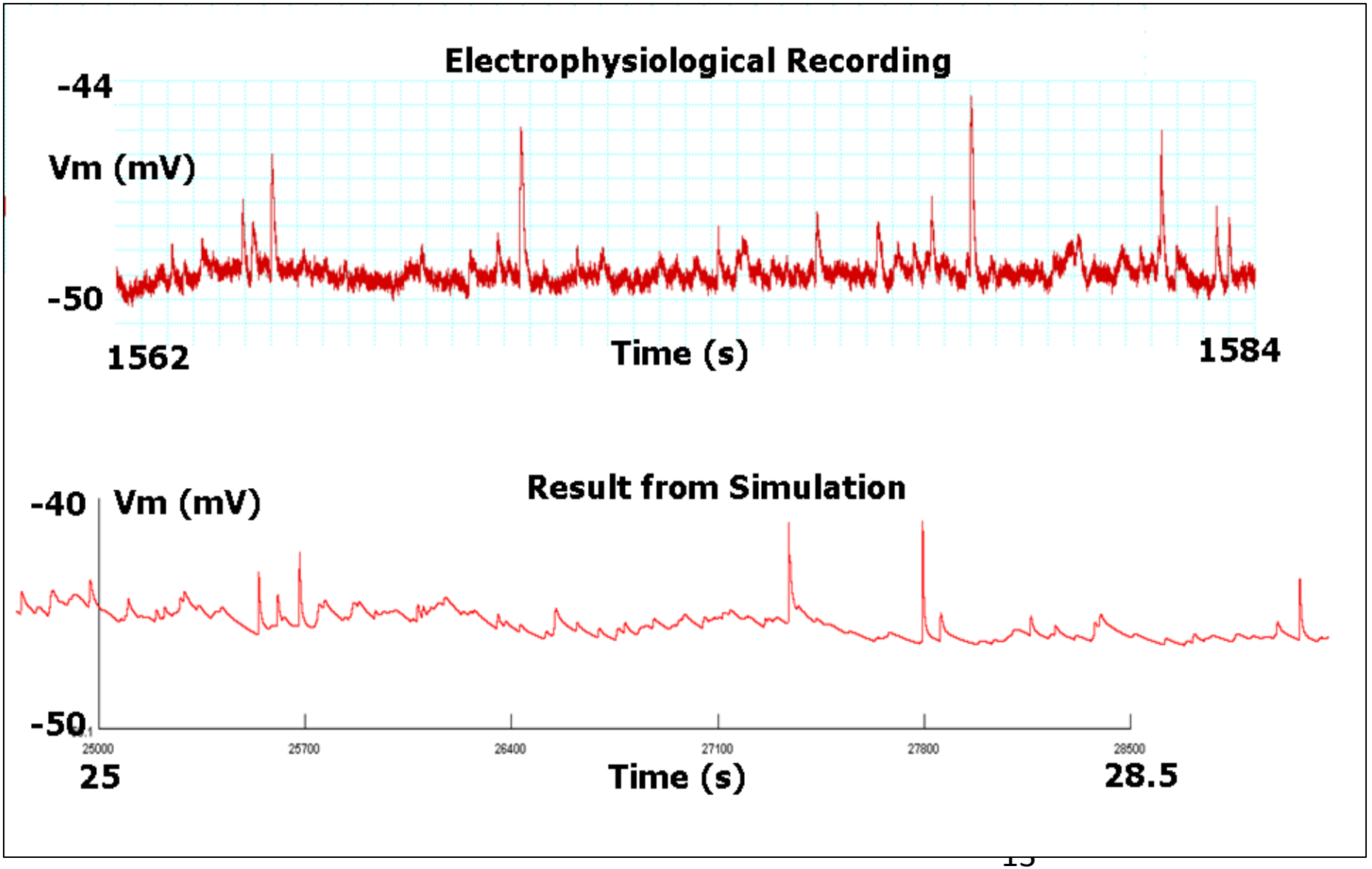
Quantity	Symbol	Value	Reference
Cell Length	L	200 µm	Fry et al. (1999)
Cell Diameter	Diam	6 µm	
Membrane Resistivity	R_m	138 kΩ.cm^2	
Total Intracellular Resistivity	R_a	608 Ω cm	
Cytoplasmic Resistivity	R_a	181 Ω cm	
Resting Membrane Potential	V_{rest}	-50 mV	Klockner and Isenberg (1985)
Specific Membrane Capacitance	C_m	1 µF/cm^2	*Standard Value*
Leakage Potential	e_pas	-50 mV	follows from V_{rest}
Leakage Conductance	g_pas	1/138000 S/cm^2	follows from R_m
Gap Junctional Conductance	g	30 nS	Estimated

Overlays: neurotransmission, active channels, Ca dynamics



Neurotransmission: modelling
“synaptic drive”

How far have we got?



What remains

- Active channels
- Ca dynamics
- Integration

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Thanks:

People

- Dr K.L. Brain
- Shailesh, Chitaranjan, Mithun, Rashmi, Vijay

Agencies

- UKIERI
- DBT

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Technical Progress

- Electrical model of detrusor syncytium, developed in NEURON, nearing completion.
- MS being prepared – along the lines of a technical report announcing the successful use of NEURON to build a syncytium.
- Detrusor spike model construction under way. Plausible spike model hopefully on hand in a few months.
- Neurotransmission: multi-point synaptic drive model put in place that mimics time-series of STDs in experimental recordings
- Ca dynamics model initiated