Synthetic and Natural Analog Computation in Living Cells

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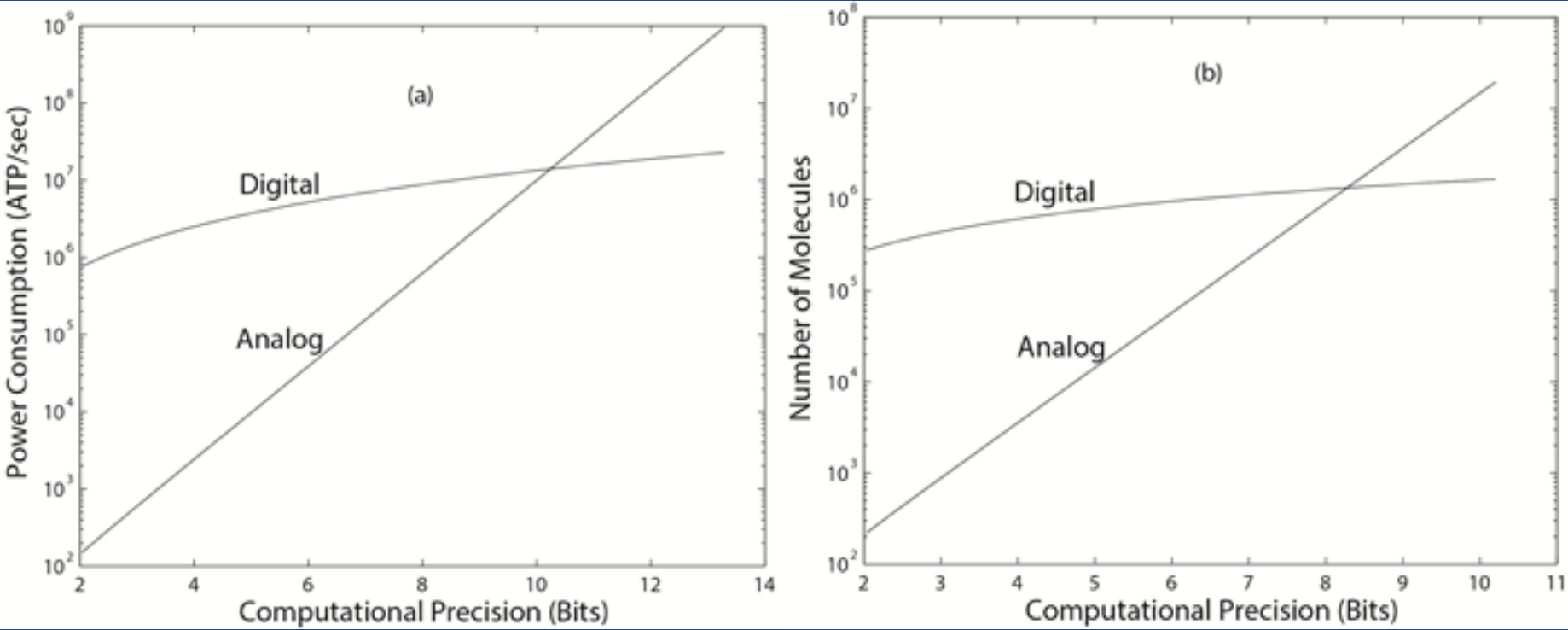
Bits to Biology, CBA
May 1st 2014

ANALOG	DIGITAL
1. Compute on a continuous set of numbers, e.g., [0,1], graded protein production from low to a maximum level.	1. Compute on a discrete set, e.g., {0,1}, protein produced at a maximum level or not present at all.
2. The basis functions for computation arise from the physics and chemistry of the computing devices such that the amount of computation squeezed out of a single genetic, RNA, or protein circuit is high.	2. The basis functions for computation arise from the mathematics of Boolean logic such that the amount of computation squeezed out of a single genetic, RNA, or protein circuit is low.
3. One wire or channel can represent many bits of information.	3. One wire or channel always represents one bit of information.
4. Computation is sensitive to the parameters of the molecular circuits.	4. Computation is less sensitive to the parameters of the molecular circuits.
5. Noise is due to thermal fluctuations in molecular devices.	5. Noise is due to round off error and temporal aliasing.
6. Signal is not restored at each stage of the computation.	6. Signal is restored at each stage of the computation
7. Robust at final and decisive outputs	7. Robust in every device and signal

R. Sarpeshkar, "Analog Synthetic Biology", *Phil Trans. Royal Soc. A*, 372:20130110, 2014

Analog vs. Digital

The relatively low-precision environment of cells makes analog computation efficient. Cells use analog and collective analog strategies to compute in an energy-efficient way.

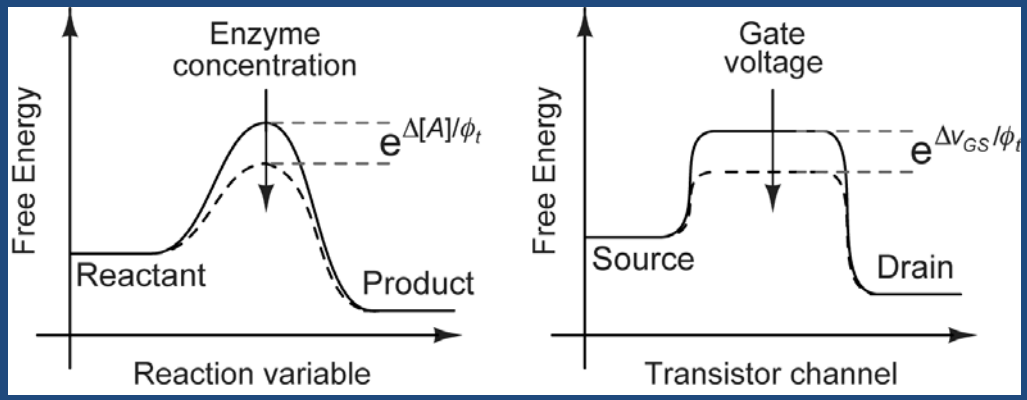


R. Sarpeshkar, "Analog Synthetic Biology", *Phil Trans. Royal Soc. A*, 372:20130110, 2014

The Cytomorphic Mapping Between Analog Chemistry & Analog Electronics

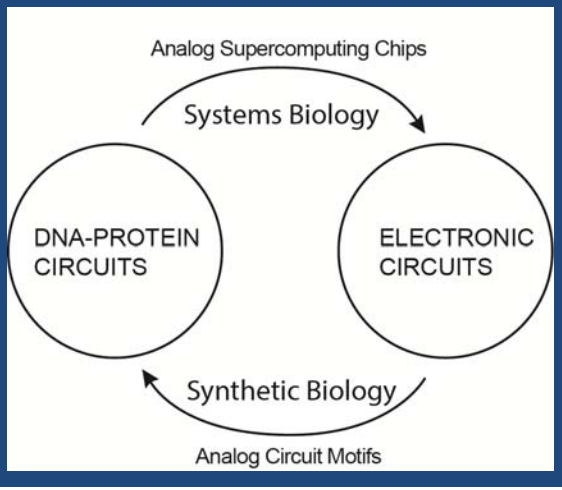
Chemistry	Electronics
Molecular flux	Electron flow (current)
Chemical potential	Electronic potential (voltage)
Enzyme potential exponentially controls reaction rate	Gate voltage exponentially controls current level
Flux balance analysis	Kirchhoff's Current Law (KCL)
Thermodynamic energy balance	Kirchhoff's voltage law (KVL)
Stochastics of molecular shot noise	Stochastics of electronic shot noise

The Cytomorphic Mapping



Log(molecular concentration)+Energy = Log(current) + Voltage
= Electrochemical Potential

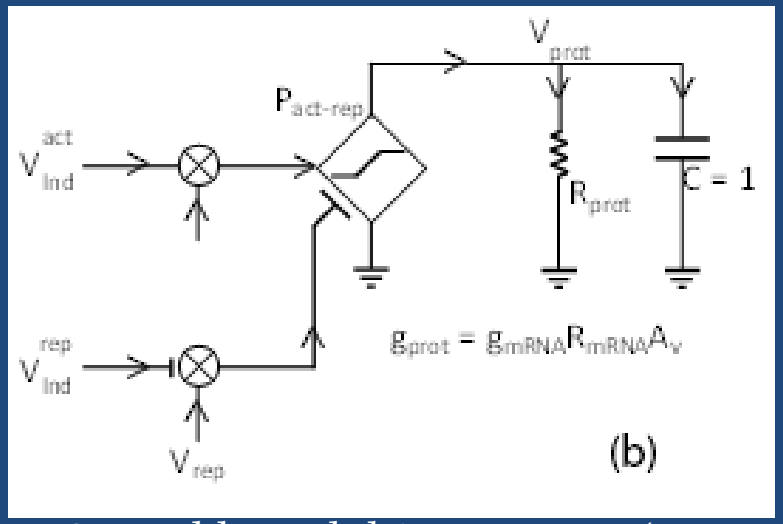
Cytomorphic Systems



R. Sarpeshkar, *Ultra Low Power Bioelectronics*, Cambridge Univ. Press, 2010

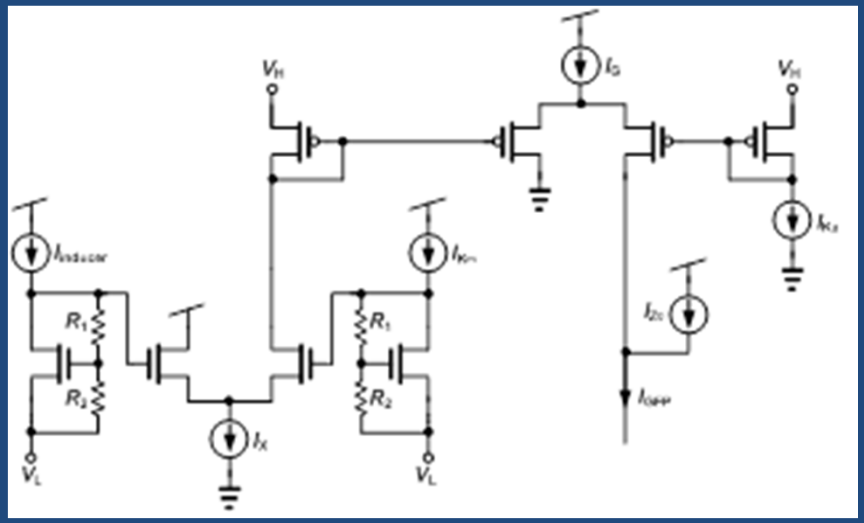
Cytomorphic Systems

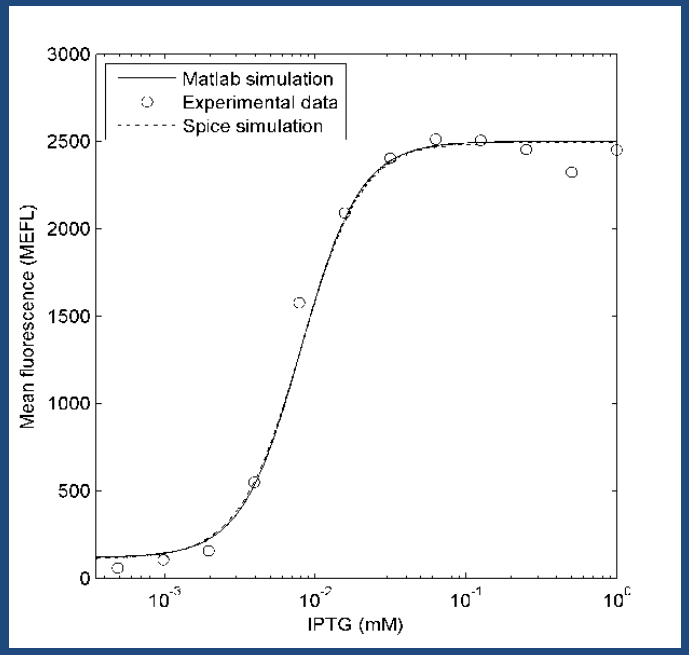
DNA-Protein Circuit



R. Sarpeshkar, Phil. Trans. Roy. A, 2014

Electronic Circuit

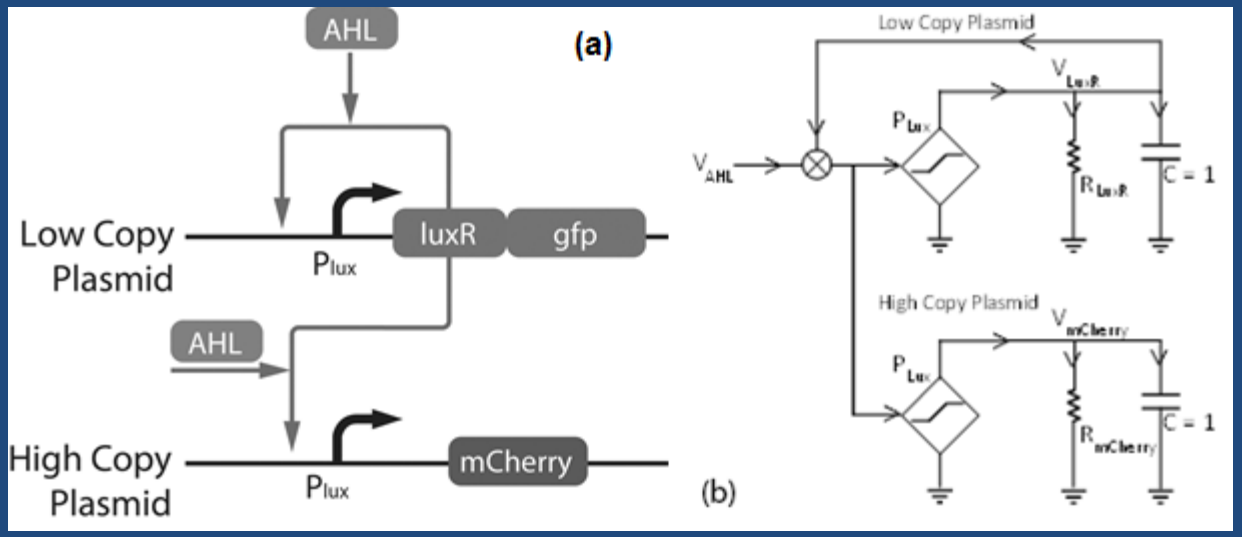


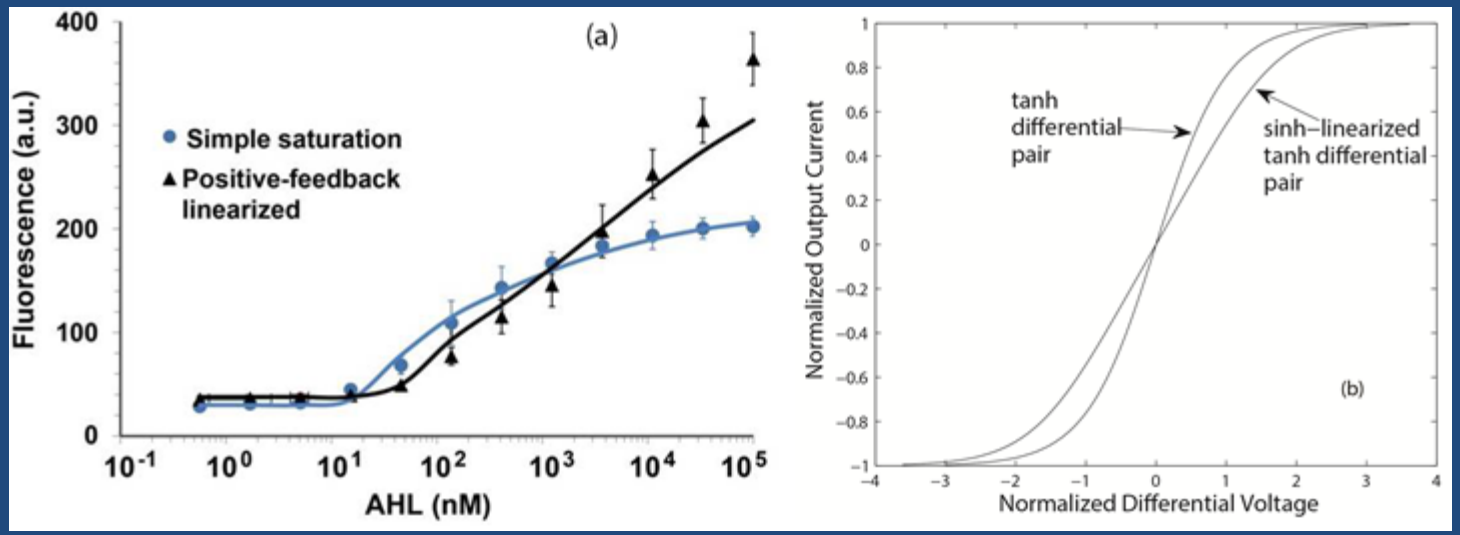


Daniel et al, "Analog Transistor Models of Bacterial Genetic Circuits", 2011 BioCAS, pp. 333-336, 2011

Experimental data from *E. coli* bacterium

Linearizing Saturating Circuits with Synthetic Analog Positive Feedback

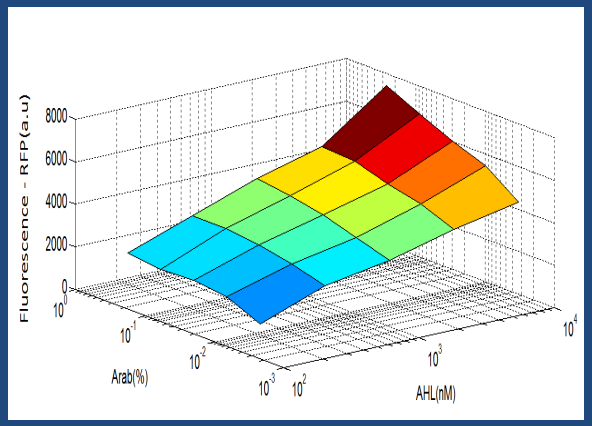




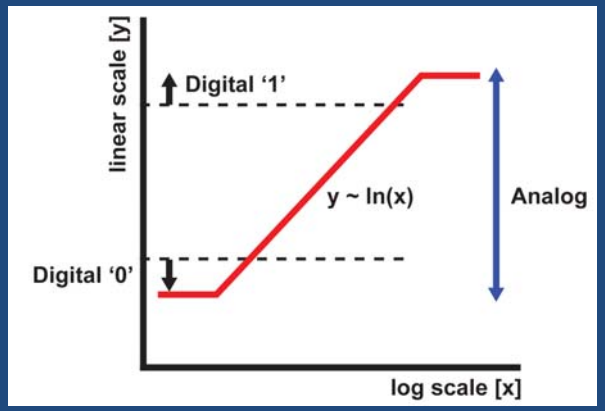
Tavakoli and Sarpeshkar, IEEE Journal of Solid State Circuits, Vol. 40, No. 2, 536-543, 2005

Daniel et al, NATURE, doi:10.1038/nature12148, May 2013

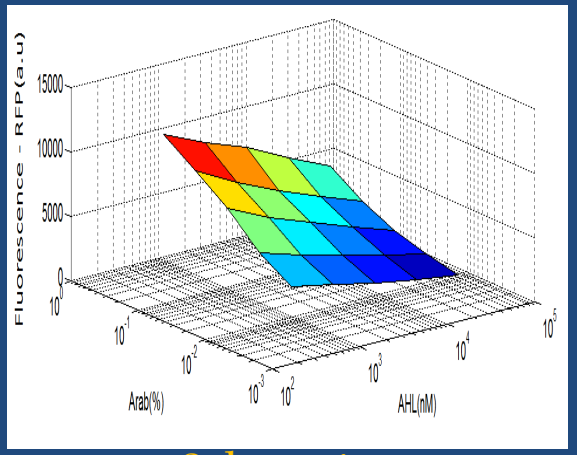
A 3-gene 'Biological Slide Rule' in Living Cells



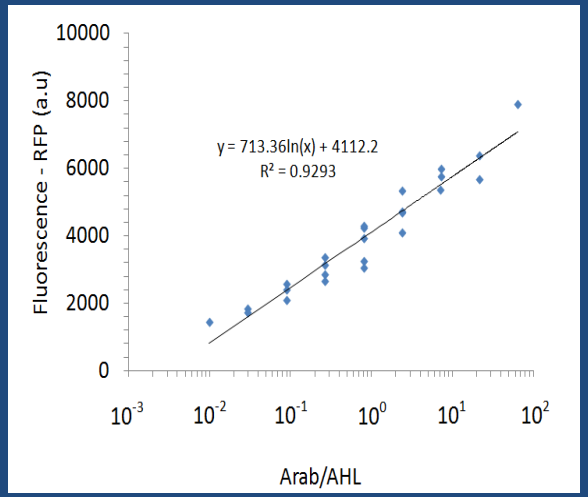
Addition



Digital Computation is a Special Case of Analog Computation

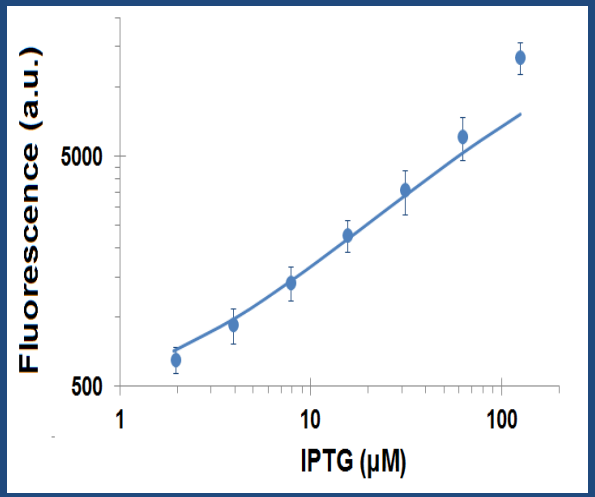


Subtraction



Division

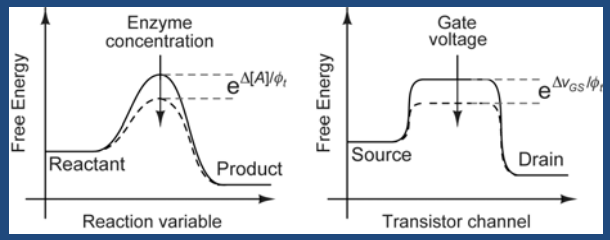
1. Enables complex computation with 65x fewer parts than a prior in-vitro digital system.
2. Enables fine analog control of gene expression.
3. Wide dynamic range molecular sensing over four orders of magnitude.

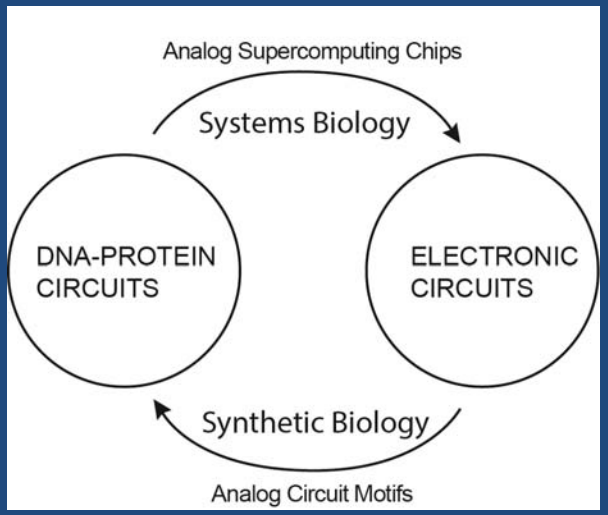


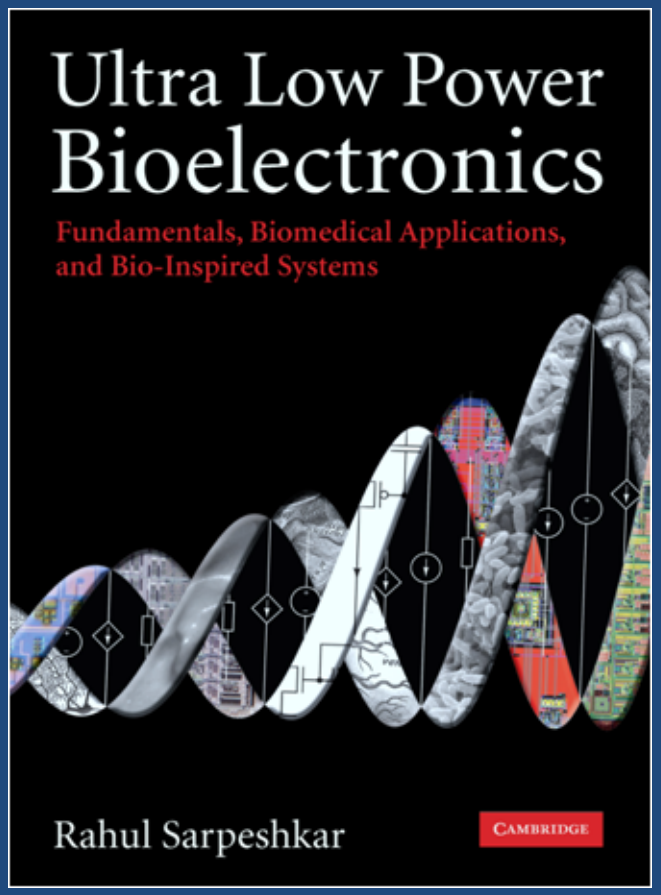
Square Roots & Power Laws

Daniel et al, NATURE, doi:10.1038/nature12148, May 30th 2013

An Analog Computation Approach to Biology







Acknowledgements:

Ramiz Daniel
Soumyajit Mandal
Sung Sik Woo
Tim Lu
Jakub Rubens
Jaewook Kim
Anne Ziegler
Wei Tong
Lorenzo Turicchia
Benjamin Rapoport

Sponsors:
Lincoln Labs, NSF, SRC

1. R. Sarpeshkar, *Ultra Low Power Bioelectronics,* Cambridge University Press, 2010.
2. Daniel et al, Analog Transistor Models of Bacterial Genetic Circuits, Proc. BioCAS, pp. 333-336, 2011.
3. Daniel et al, Synthetic Analog Computation in Living Cells, doi:10.1038/nature12148, May 30th 2013
4. R. Sarpeshkar, "Analog Synthetic Biology", Phil. Trans. Roy. A 372:2013.0110, 2014

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