Energy, Information, and Power in Cells

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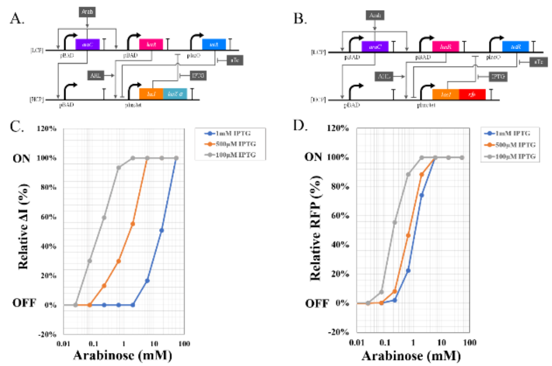


Problem / Objective

(1) Identify 10+ Universal Principles for Bio-inspired Ultra-Energy-Efficient Information Processing from Molecule to Brain;(2) Measure Power-Speed-Precision and Energy-Information Tradeoffs in Microbial Cells. (3) Measure and Quantify the first ATP Atlas Of the Cell.

Technical Approach

Creation of Synthetic Microbial Circuits with Sensitive Electrical Reporting and Feedback; Measurement of ATP in Cells; Measurement of Power, Speed, and Precision in Cells; Circuit Modeling of Molecular Pathways in Cells

Uniqueness

- Energy-Efficient Synthetic Circuits in Cells; Controlled Probiotics for adaptive and intelligent medicine**;** Metabolic Engineering.
- Human-Performance Enhancers via ATP-based Molecular Insights; Universal Energy-Efficient Design Principles from Molecule to Insect/UAV Flight.

Description of Research

1. Developed a sensitive all-electrical molecular reporting system in living cells, useful for quantifying the costs of information and power in synthetic and natural cellular circuits; 2. Developed an ATP reporter system in cells that monitors ATP levels in cells in real time, which is useful for making all synthetic-biological circuits adapt to metabolic burden and relate energy, information, and power through fundamental quantitative relationships; 3. Developed circuits to model quantitative relationships between nutrients, metabolism, and ATP in cells; 4. Showed how analog circuits can help design sophisticated cell-population and cell-type control feedback systems; 5. Showed how the design of novel Bio-OpAmps and other synthetic biological circuits can be automated in the future with cytomorphic silicon chips.

Accomplishments

- **Publications:** 1) J. Zeng, A. Banerjee, J. Kim, Y. Deng, T. Chapman, R. Danial, and R. Sarpeshkar, “A Novel Bio-electronic Reporter System in Living Cells Tested with a Synthetic Biological Comparator”, NATURE Scientific Reports, doi:10.1038/s41598-019-43771. 2) J. Teo, R. Weiss, and R. Sarpeshkar, “An Artificial Tissue Homeostasis Circuit Designed via Analog Circuit Techniques”, *IEEE Trans. on Biomed. Circs. And Systems,* Vol. 13, No. 3, June 2019.

- **Presentations:** Design and Rapid Emulation of a Synthetic Microbial Operational Amplifier on Cytomorphic Silicon Chips, J. Teo, J. Zeng, S. Woo, and R. Sarpeshkar, Synthetic Biology: Engineering, Evolution, Design, NYC, June 2019.

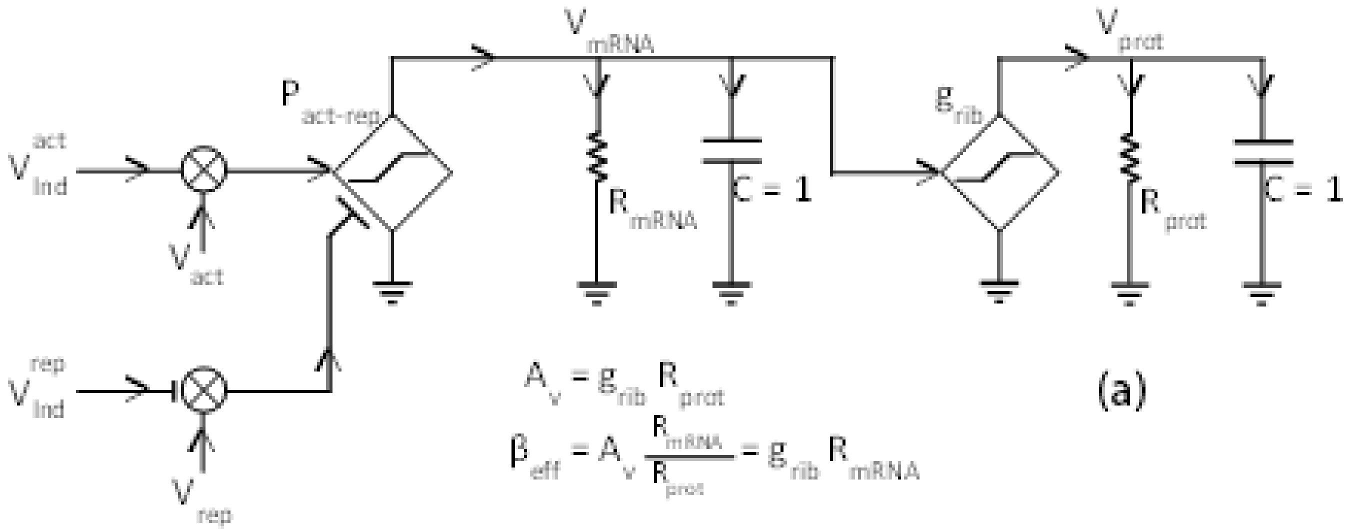
Peers and Collaborators

- R. Weiss; R. Danial

Ten Information Based Principles for Ultra-Energy-Efficient Processing [1]

Principle	Neural Information Processing	Cellular Information Processing	Bio-inspired Processing
1. Efficient Encoding of computation in basis functions of physical and chemical devices	Encode multiplication via biochemical binding of a neurotransmitter to a gated ion-channel at a synapse.	Encode multiplication via biochemical binding of enzyme and substrate in a chemical reaction.	Encode convolutional multiplication in an efficient resistive grid in a silicon retina [12]. A bio-inspired RF cochlea encoded traveling-wave computation in distributed inductors and capacitors and created the fastest spectrum analyzer known to man, outperforming the Fast Fourier Transform [13] in its scaling.
2. Exploit the efficiency of Boltzmann Physics	Optimally energy-efficient spike-rate coding is a Poisson exponential distribution, seen at high rates in neurons [14, 15]	Rates of reactions are governed by Boltzmann exponentials and exploited in reaction networks.	Exponential sub-threshold operation of transistors and associated log-domain computation create optimally efficient dynamical systems and filters for many applications [1]
3. Optimal amount of analog preprocessing before digitization	Dendrite cannot be too long before a spiking decision is made or the decision will be unreliable; but, it cannot be too short or the efficiency of analog computation will not be exploited [8, 10].	Analog protein networks with the right logical depth pre-process signal before a digital genetic decision is made [1].	Compressed Sensing with preprocessing of analog sensor information before a high-level bit is reported occurs at an optimum amount of compression, e.g., in the optimal number of stages in a silicon cochlea reporting spiking outputs [1]
4. Highly Parallel Processing	Neuronal Networks	Biochemical Reaction and Genetic Networks	Cellular Automata, Silicon Retinas and Silicon Cochleas [1, 12]
5. Balance Computation and Communication Costs	Axon diameter must be optimized to support the needed rate of computational information transfer, which must be optimally matched to the spike output rate of underlying neurons [10, 11, 16].	Transcription-Factor network fan-out and fan-in must be commensurate with needed precision and needed tolerance for crosstalk [1, 17].	Preprocess raw sensor information such that radio transmission bandwidth is reduced but not at the cost of high preprocessing power, e.g., in advanced sensor networks with compressed sensing [1, 8, 9, 18].
6. Use Collective Analog and Hybrid Analog-Digital computation with many interacting moderate-precision components to do arbitrarily precise or arbitrarily complex computation [1, 4, 8, 9]	10 ms inter-aural time differences are perceived by the auditory system even though the timing jitter of any individual fiber in the auditory nerve is ~1ms. The brain's architecture also scales because of this principle [1, 8].	Transcription-Factor networks make collectively reliable decisions even though each transcription factor is noisy, e.g., in cascaded decisions for cell differentiation and growth. These decisions eventually lead to the remarkably robust self-assembly of a whole human baby from nearly 47 cell divisions [1, 17]	A Spiking-Neuron Inspired Collective Analog Adder adds arbitrarily precisely even though each individual analog component is only 4-bit precise [3]:16-bit precise addition via four 4-bit-precise Kirchoff's-Current-Law adders was demonstrated.
7. Reduce the amount of information that needs to be processed	The retina compresses almost 36 Gbs^{-1} to 20 Mbs^{-1} in the optic nerve such that the brain's visual-cortex energy consumption is kept within bound [1, 15].	Convergent cell - signaling networks preprocess and compress multiple sensor inputs to generate one protein output that leads to cellular action [17].	An ultra-low-power analog bionic ear processor reduced the amount of information needed to be processed digitally thus drastically reducing power consumption in a state-of-the-art cochlear-implant processor [18, 19].
8. Use Feedforward and Feedback architectures to reduce signal noise and device noise and to amplify meaningful signal statistics.	Balanced excitation and inhibition leads to more informative spikes, thus leading to optimal energy efficiency in neuronal coding [21]. Feedforward and Feedback Compensation is common in insect flight control [20] and VOR-based head-eye saccades [1].	Feedforward Loops (FFLs) are the most dominant circuit motif in all microbial genetic circuits [17]. There is ubiquitious use of negative and positive autoregulation to improve performance in DNA-RNA-protein networks; mitochondrial Ca^{2+}-based increase in ATP occurs during muscular activity or neural signaling [22].	Feedforward and feedback spiking-neuron-inspired analog-to-digital converter was the world's most energy-efficient analog-to-digital converter ever built at the time of its creation [23].
9. Never operate with speed and precision simultaneously.	Neuronal threshold circuits and all comparators obey this principle while linear amplifiers do not [1].	Genetic comparators in cell-cycle regulation obey this principle [17].	A bio-inspired predictive comparator with adaptive gain control obeyed this principle and yielded more than an order-of-magnitude reduction in the energy needed to react for a given delay [37].
10. Operate slowly and adiabatically.	Dendritic amplification is energy efficient due to graded analog changes that slowly build the signal along the dendrite, just like cochlear amplification, or distributed gain amplification in photoreceptors [1, 24]	Mitochondrial electron transport chains achieve efficiency near the fundamental limits of physics due to adiabatic electron transport over multiple Complex I —IV enzymes that slowly change redox potential [25-36].	Via optimally slow electrode voltage regulation, an adiabatic energy-recycling electrode-stimulator for neural implants achieved, for the first time, the best performance that is ever possible: it operated at the fundamental limits of physics of electrode energy dissipation [38].

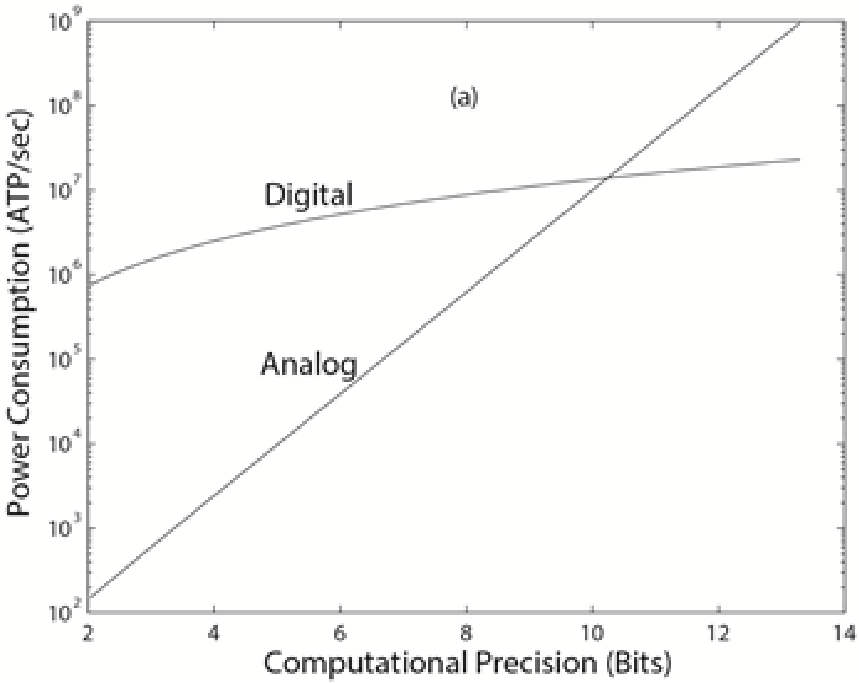
An Exact Circuit Representation of Transcription and Translation in Cells [2]

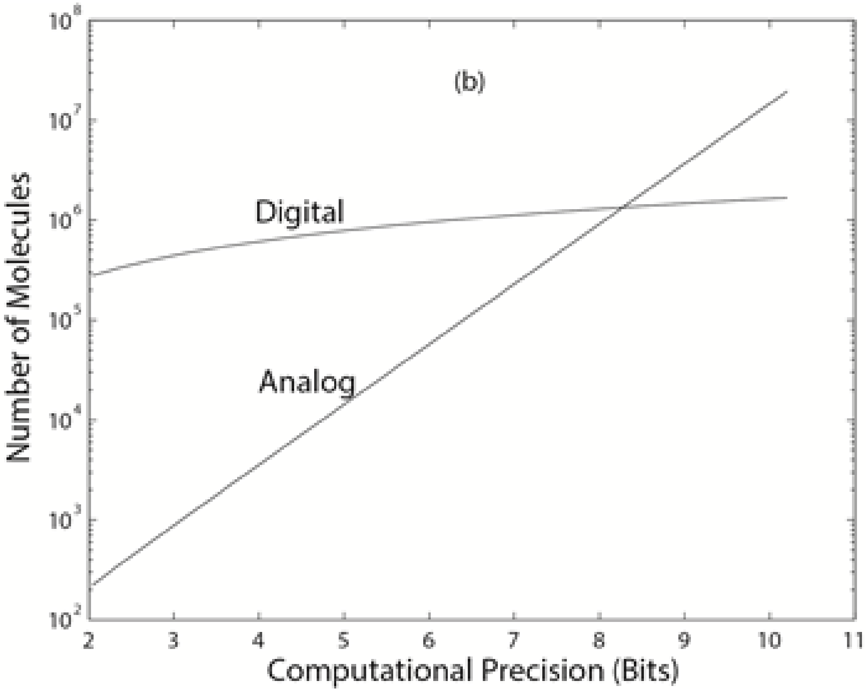


$$A_v = g_{rib} R_{prot}$$

$$\beta_{eff} = A_v \frac{R_{mRNA}}{R_{prot}} = g_{rib} R_{mRNA}$$

ATP Consumption and the Number of Molecules increase when information is processed more precisely in either Analog or Digital Computation in Cells [2]





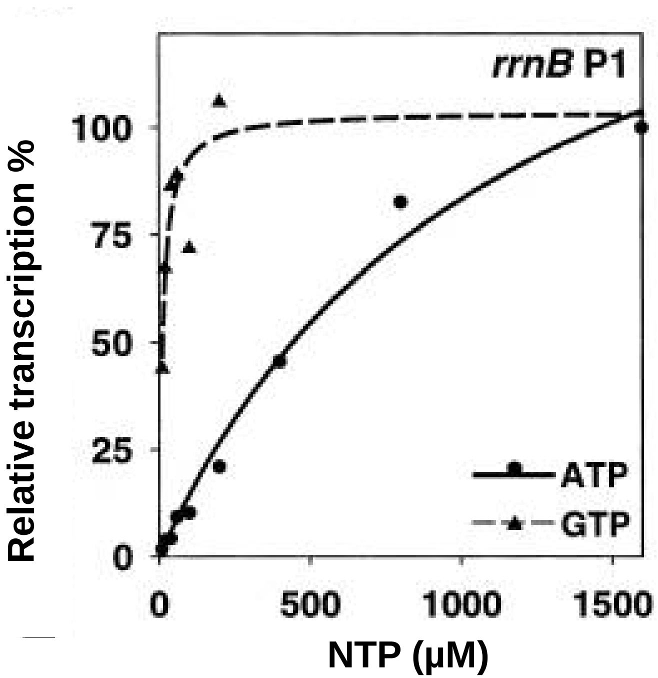
$$N_{prot} = (\beta_{eff} + 1) S_N$$
$$N_{mRNA} = \frac{N_{prot}}{A_v}$$

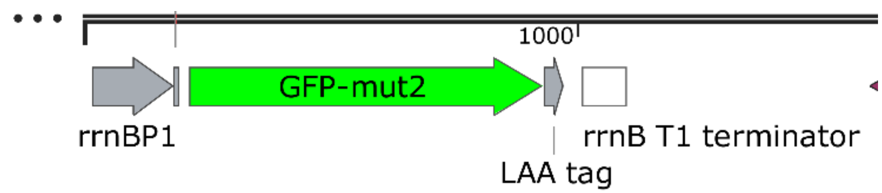
$$P_{prot} = \frac{S_N}{\tau_{prot}} (\beta_{eff} + 1)\left(\frac{E_{mRNA}}{\beta_{eff}} + E_{prot}\right)$$

$$P_{ATP} = \frac{E_{ATP\_R} N_{MRNA}}{\tau_{MRNA}} + \frac{E_{ATP\_A} N_{prot}}{\tau_{prot}}$$

Developing an ATP-sensing reporter system

- **ATP-sensing promoter: rrnB P1**
- **Developed an ATP-reporter system: rrn-GFP-LAA with a fast folding and fast degrading GFP mutant (GFPmut2) for real-time monitoring.**

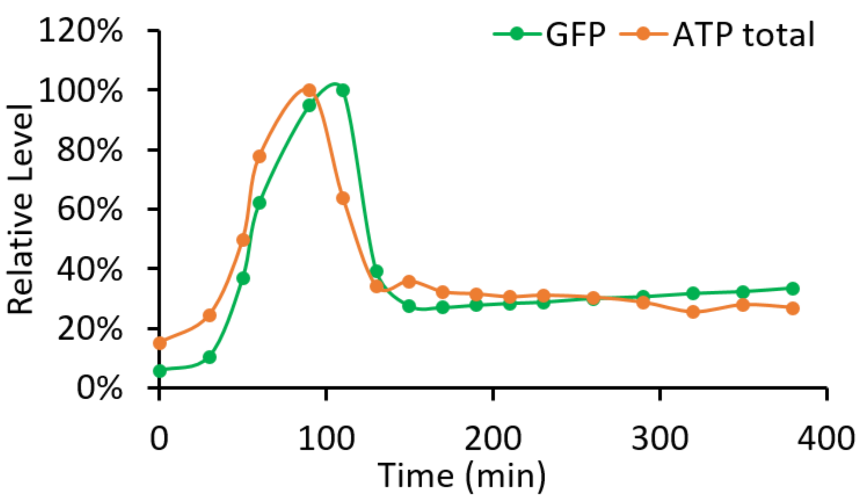




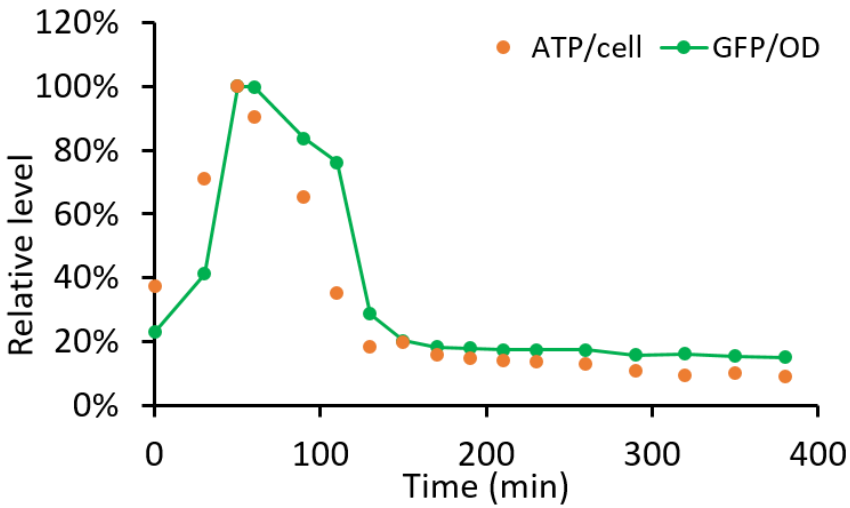
Schneider, et al, PNAS, 2002.

ATP-reporter system (rrn-GFP-LAA faithfully tracks ATP concentration)

Population level

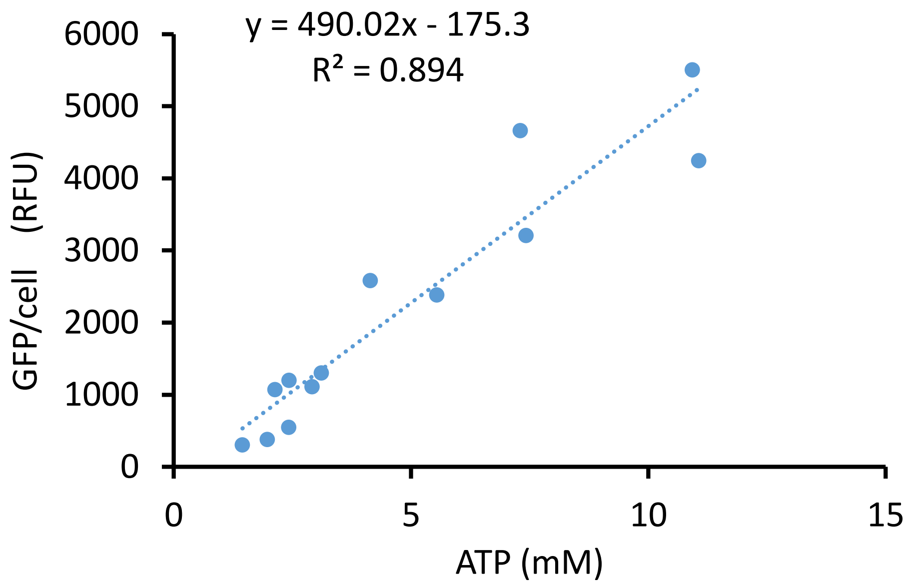


Single cell level



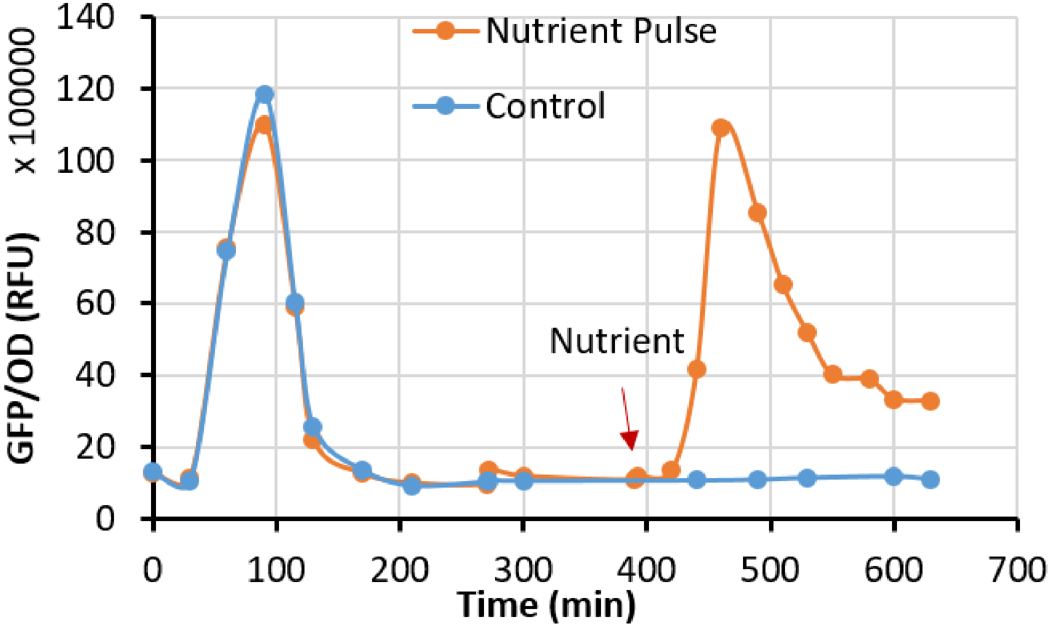
Absolute ATP concentrations were measured by the standard luciferase assay and compared to GFP signal over time.

Linear correlation of ATP-reporter system and ATP concentration in cells

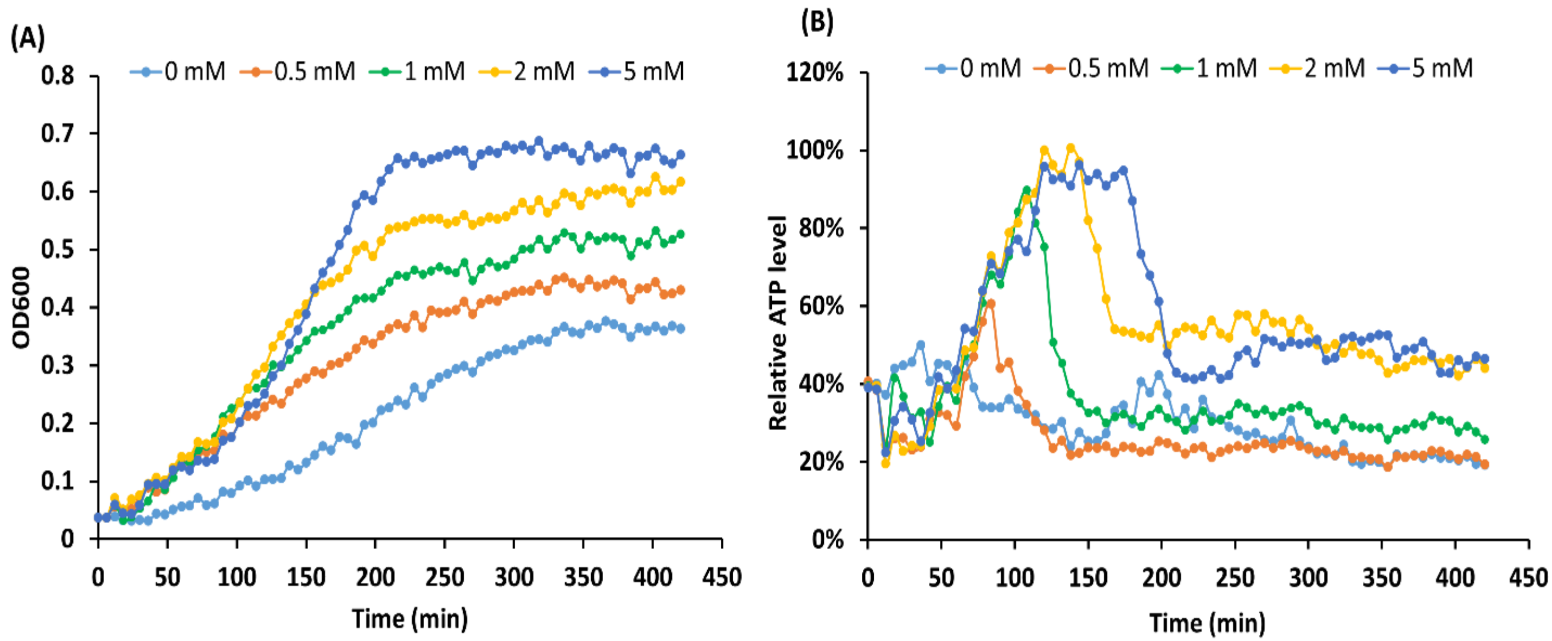


ATP-sensing promoter in response to nutrient input

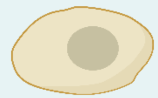
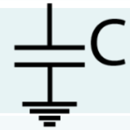
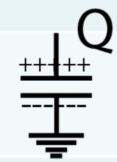
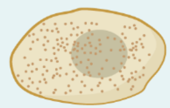
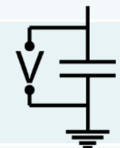
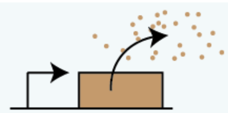
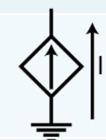
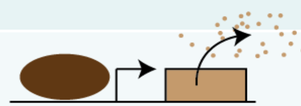
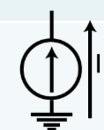
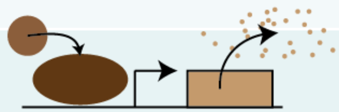
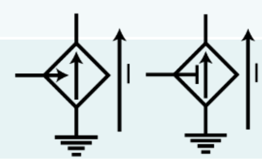
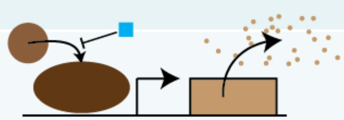
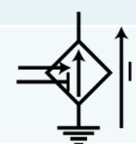
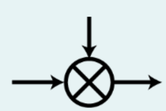
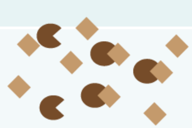
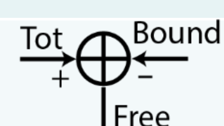
After nutrient is fully consumed, ATP drops. A new nutrient pulse triggers ATP production to a similar level as the first peak.

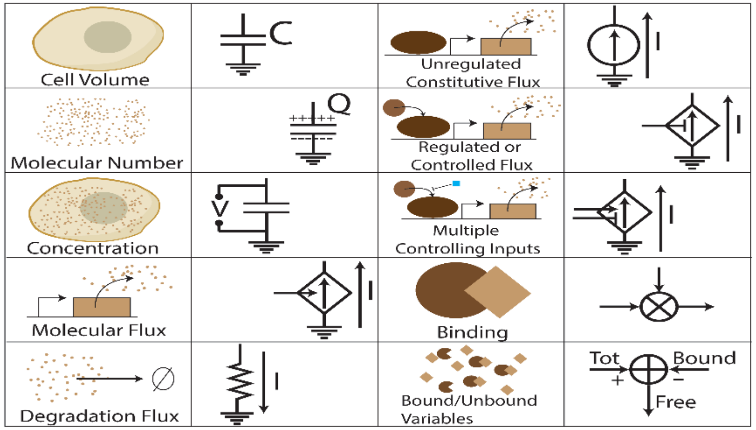


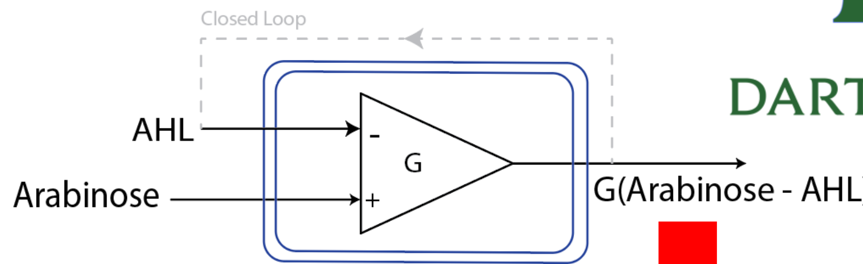
Effect of glucose on bacterial growth and ATP level

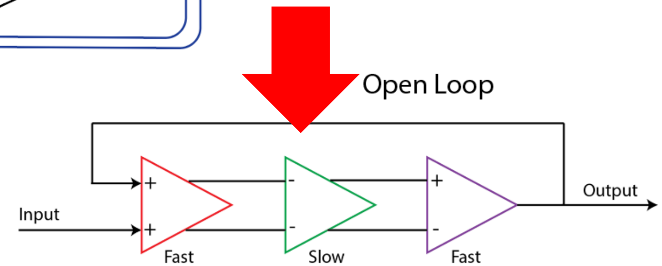


Biology to Electronics Translation Table

Biology		Electronics	Comment
Cell Volume			The capacitance helps us 'store' molecular number and concentration state just like a cell itself does.
Molecule Number			Charge = Capacitance x Voltage; Molecule Number = Concentration x Volume
Molecular Concentration			Can be RNA, Protein, DNA, or other small-molecule concentration
Molecular Flux			Can be RNA or Protein Production or Degradation for example.
Degradation Flux			The degradation can be implicit, e.g., you lose molecules as a cell divides and concentration of molecules within a cell drops due to dilution. It can be non-linear as well.
Unregulated Constitutive Flux			Always symbolized by **a circular current source**
Regulated or Controlled Flux			Always symbolized **by a diamond current source** with a control or regulating input arrow coming into it.
Multiple Controlling Inputs			Always symbolized by **a diamond current source with multiple input arrows** coming into it.
Binding of two molecules			Symbolized by a **multiplier symbol**
The concentration of free or bound variables			The ubiquitous **'use-it-and-lose-it' feedback loops.**

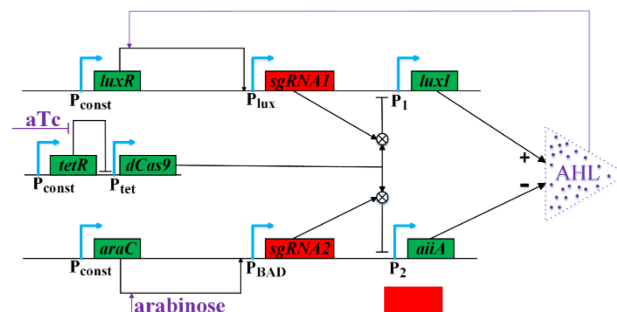


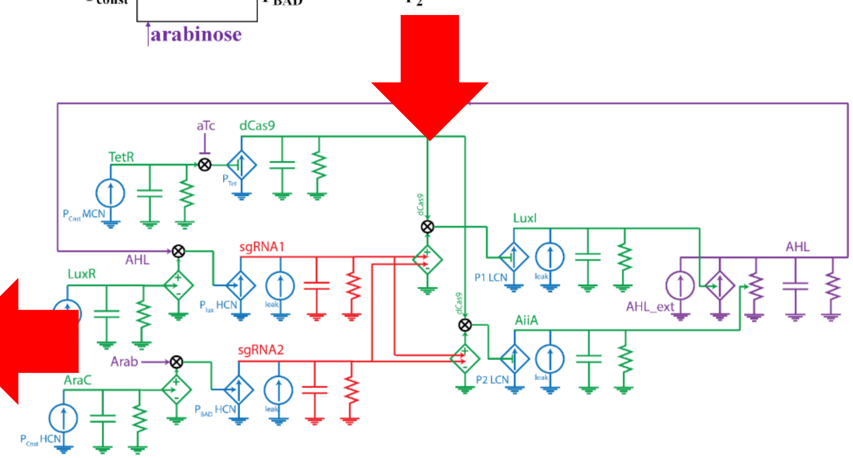


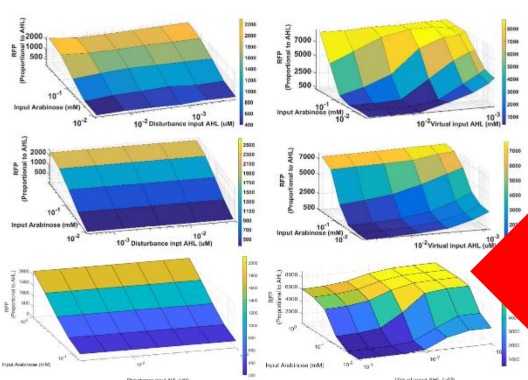


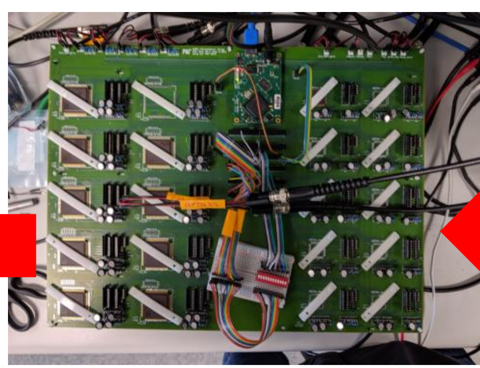
Design and Rapid Emulation of a **Synthetic Microbial Operational Amplifier** on Cytomorphic Silicon Chips

Jonathan JY Teo**, Ji Zeng, Sung Sik Woo, **Rahul Sarpeshkar

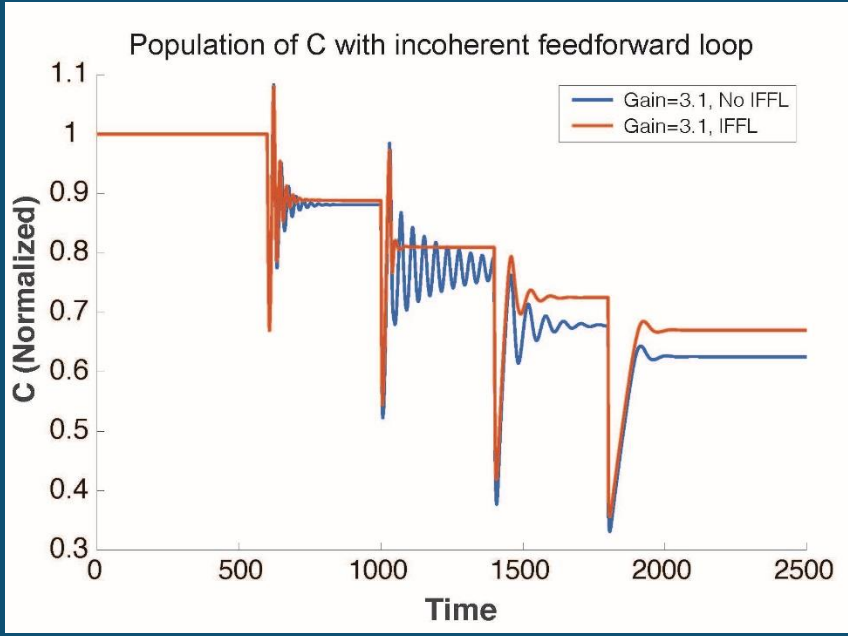


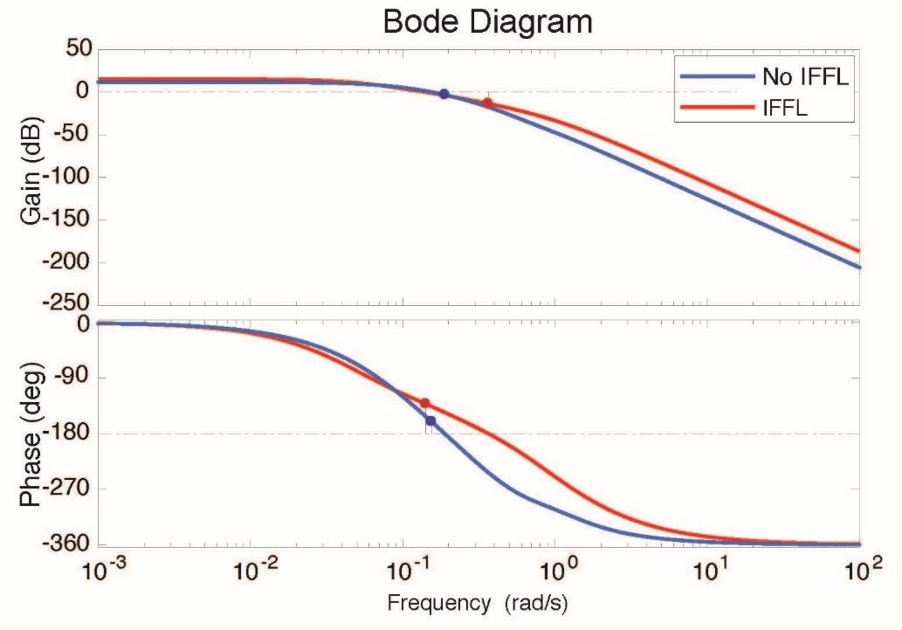






A derivative 'lead-compensated' analog circuit translates to an incoherent feedforward loop in a cell-division population-control circuit and improves stability.

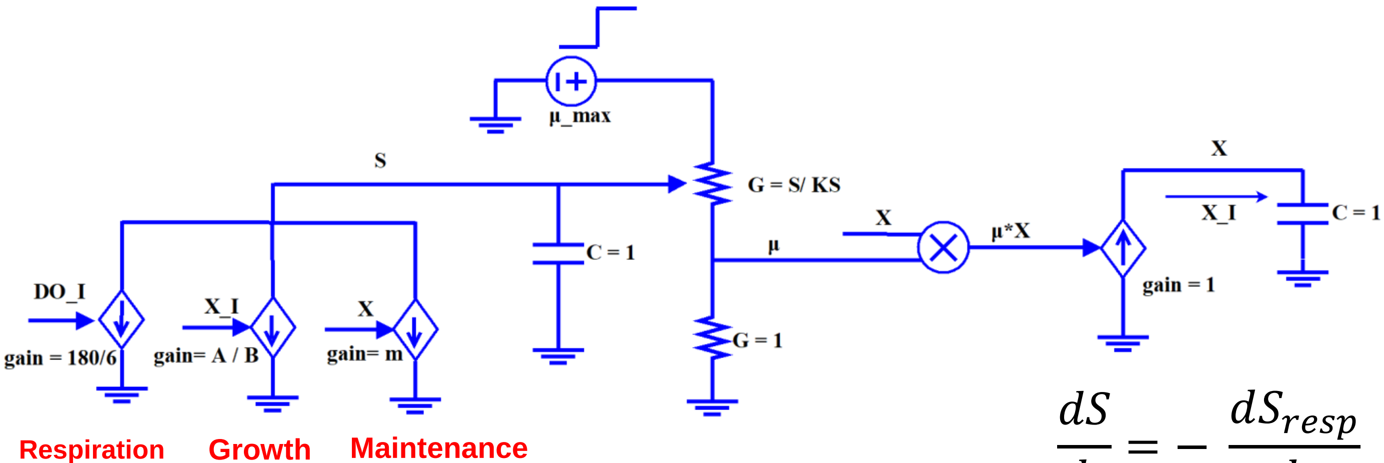




J. J. Y. Teo, R. Weiss and R. Sarpeshkar, "An Artificial Tissue Homeostasis Circuit Designed via Analog Circuit Techniques," in IEEE Transactions on Biomedical Circuits and Systems. doi: 10.1109/TBCAS.2019.2907074

Electrical circuits model growth and metabolism [unpublished]

- **A simple circuit accurately models bacterial growth and glucose consumption**

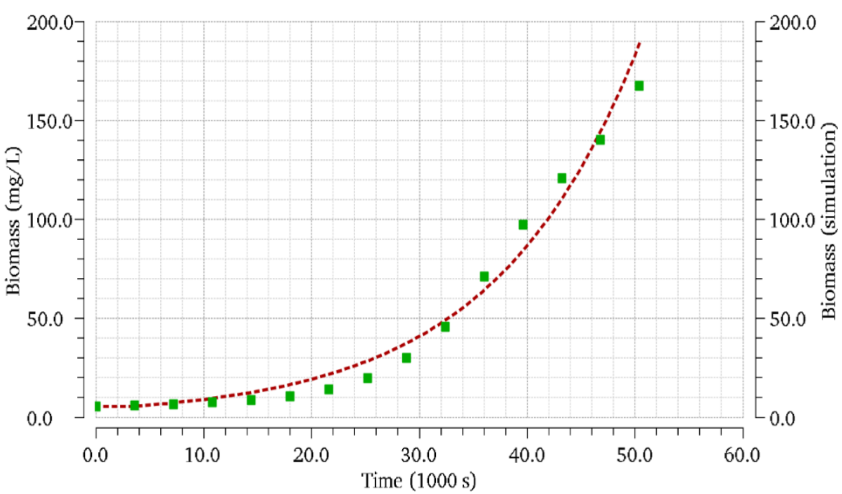


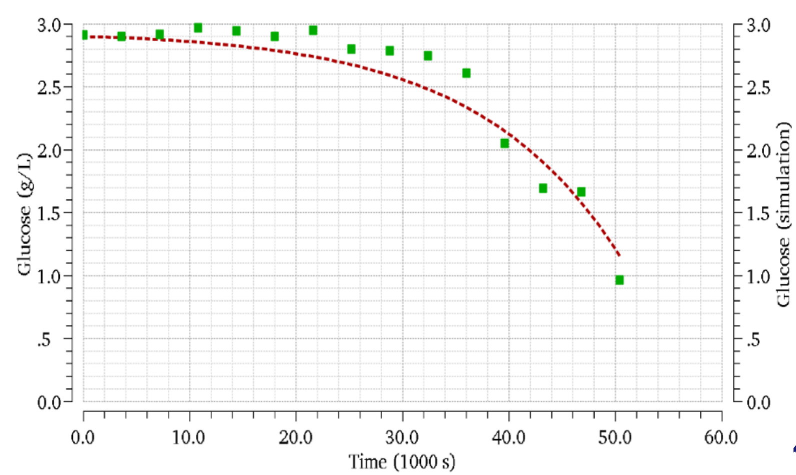
$$\mu = \mu_{\max}\frac{\frac{S}{K_S}}{1+\frac{S}{K_S}} \quad (1)$$

$$\frac{dX}{dt} = \mu X \quad (2)$$

$$\alpha\frac{dX}{dt} = \beta\frac{dS_{gly}}{dt} \quad (3)$$

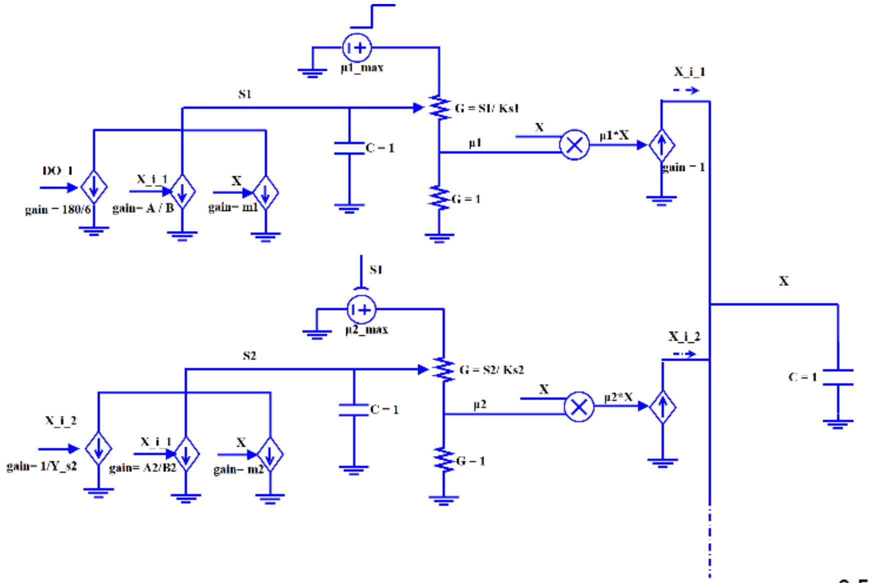
$$\frac{dS}{dt} = -\frac{dS_{resp}}{dt} - \frac{dS_{gly}}{dt} - mX = -\frac{180}{6}\frac{dO_{2,resp}}{dt} - \frac{\alpha}{\beta}\frac{dX}{dt} - mX \quad (4)$$

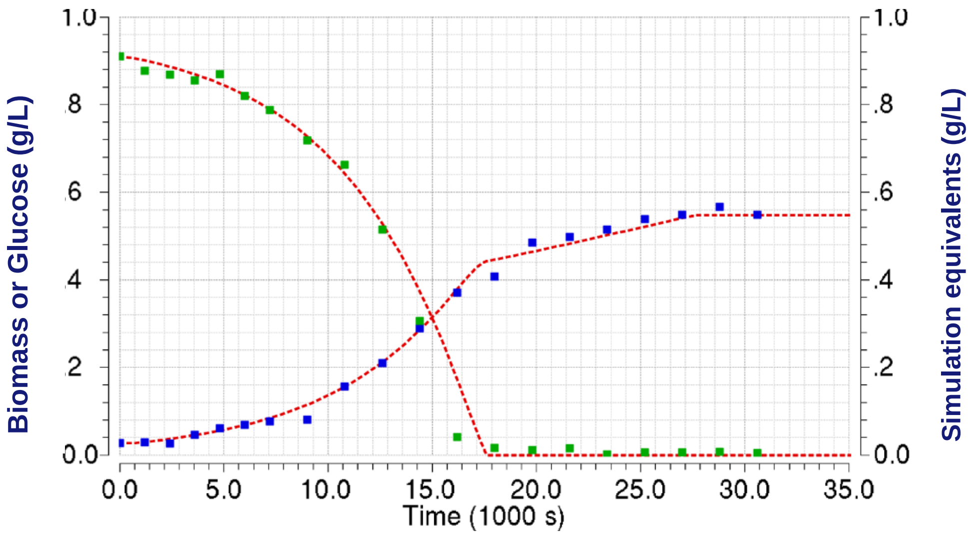




Electrical circuits model growth on multiple substrates

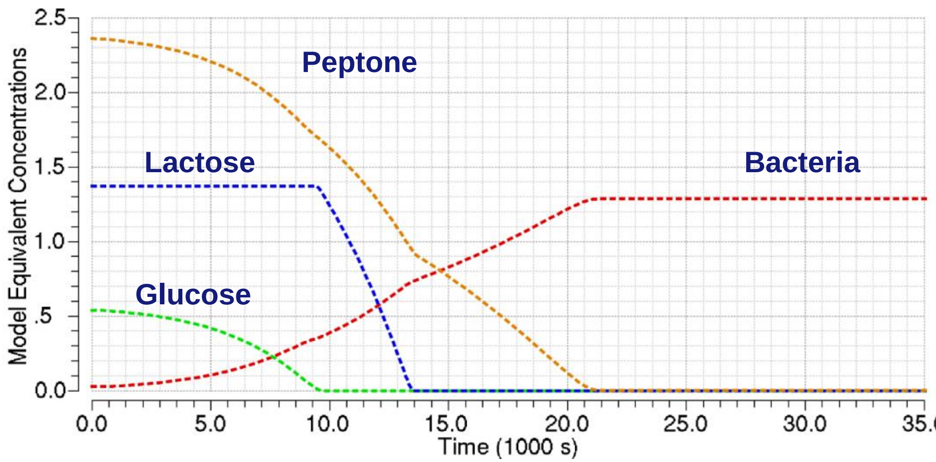
- **Dual substrate modeling and Modularity of circuits**



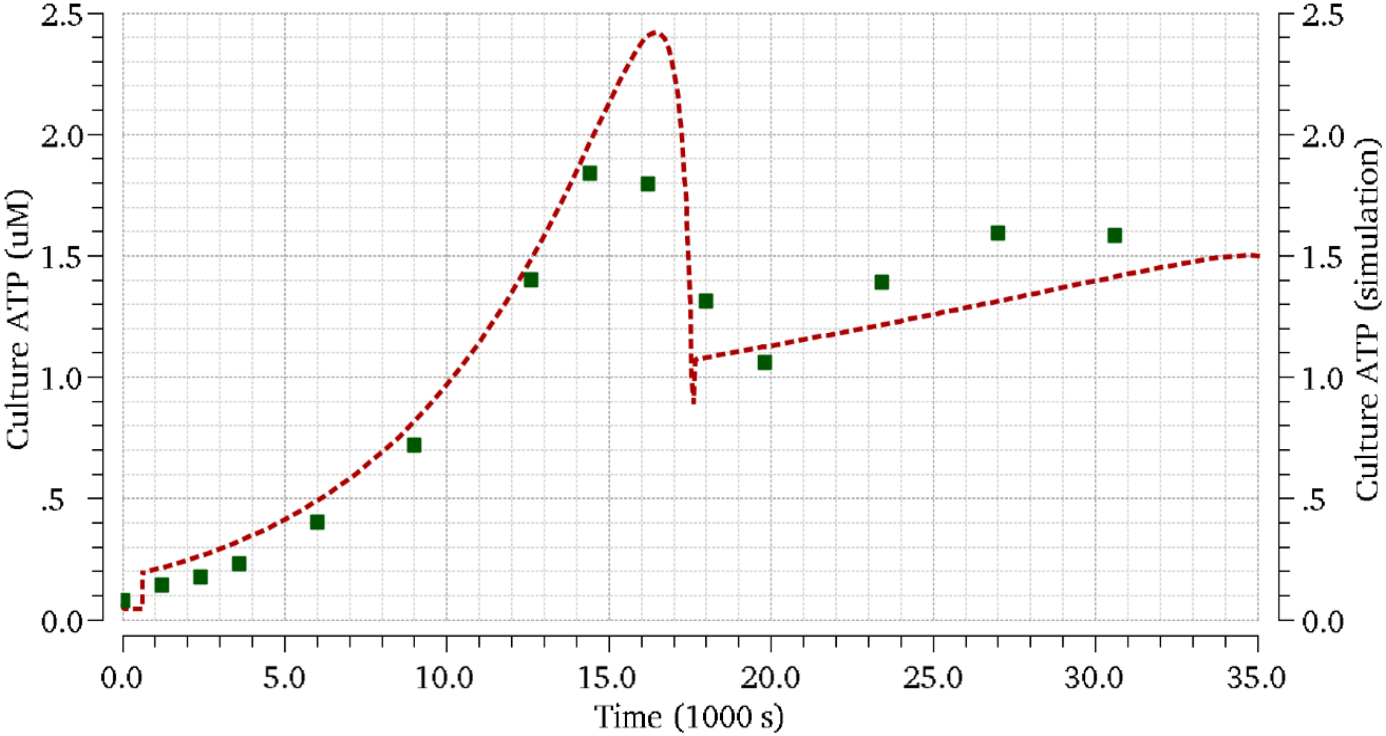


Adding more blocks

- **Multiple substrate modeling**

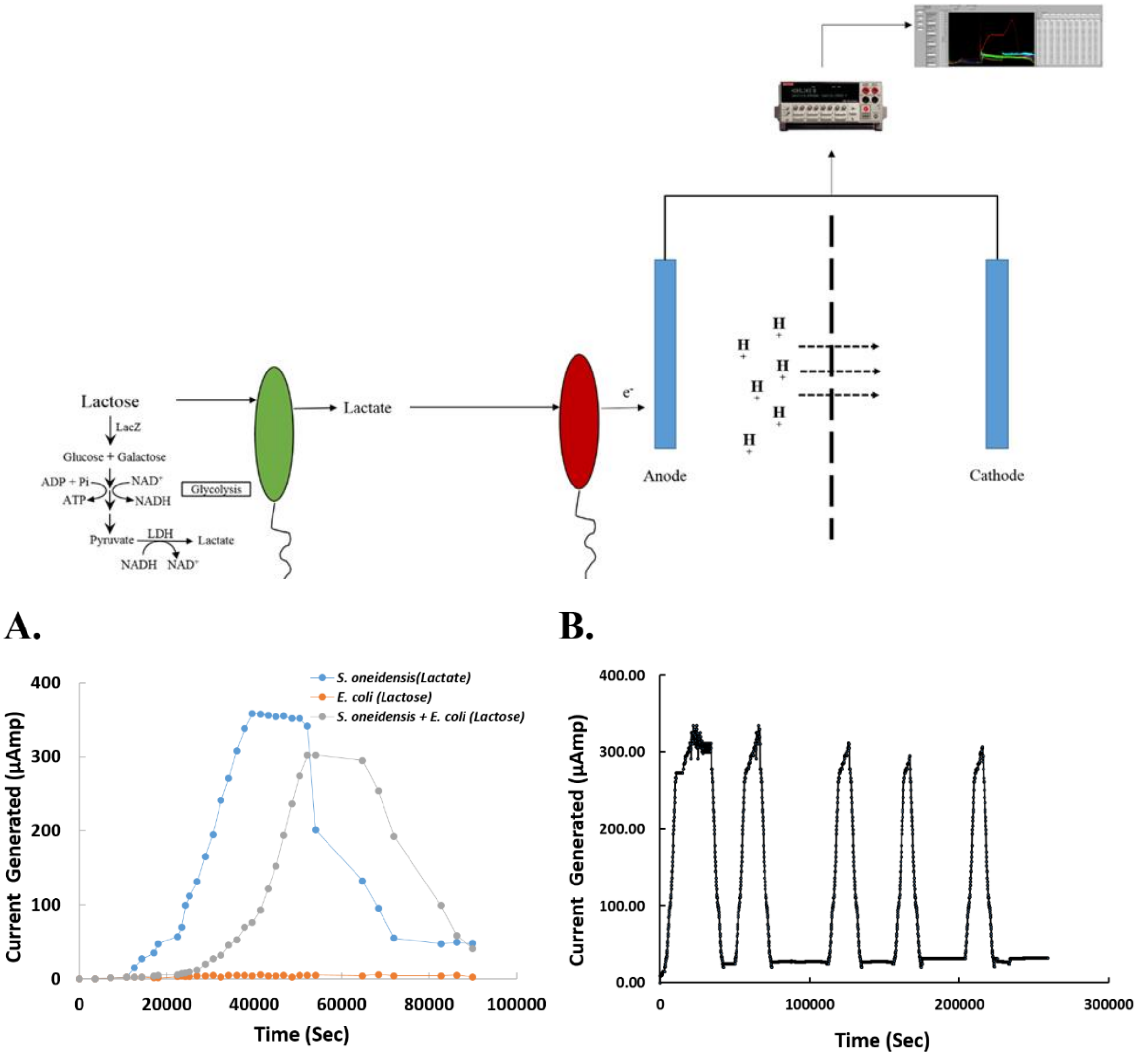


Modeling and Measurement of ATP dynamics on glucose and amino-acid substrates [unpublished]



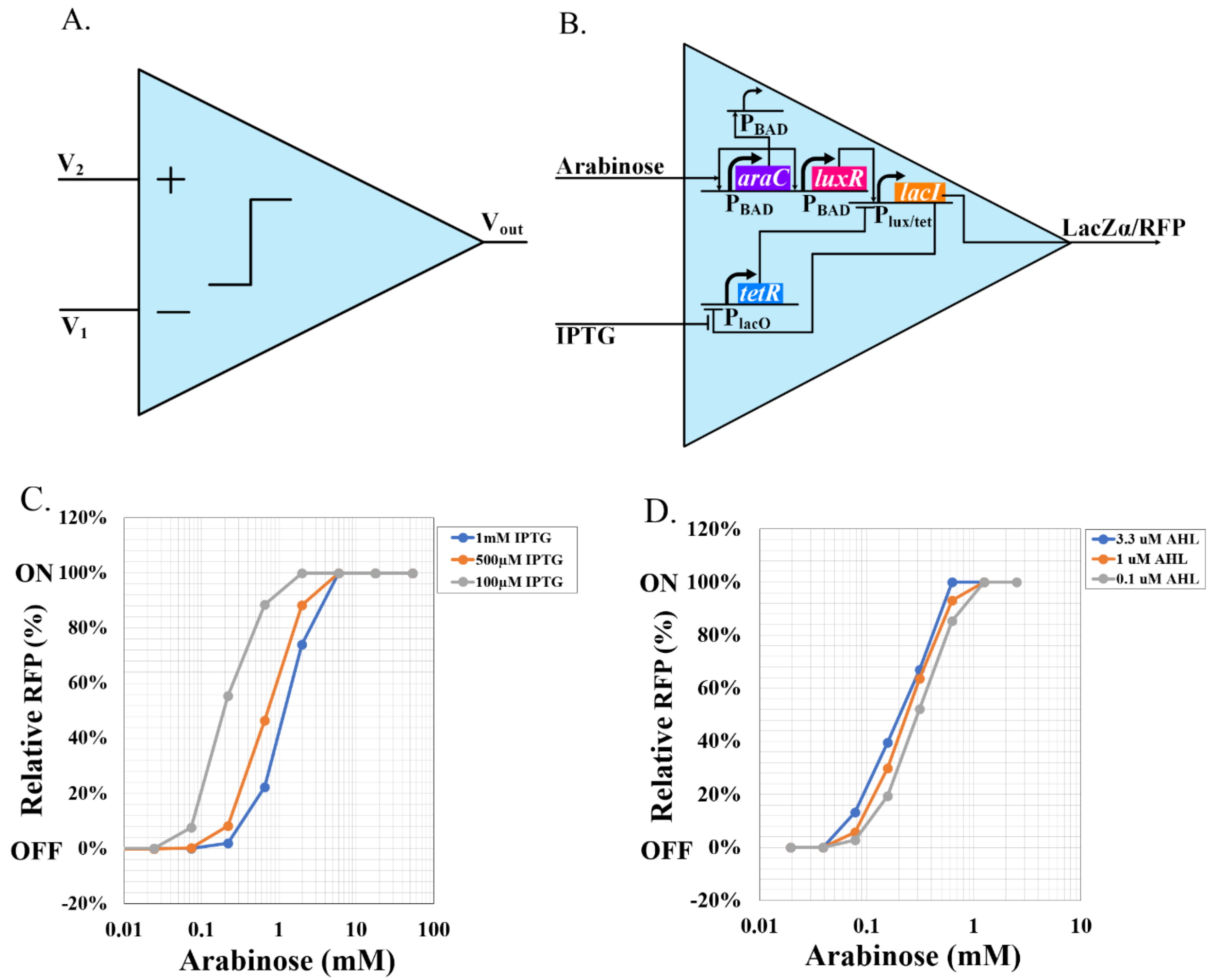
ATP was measured by a luciferase assay and fitted to our model.

Electricigenic Reporting of Molecular Concentration in Cells [54]



(Zeng et al., NATURE Scientific Reports, 2019)

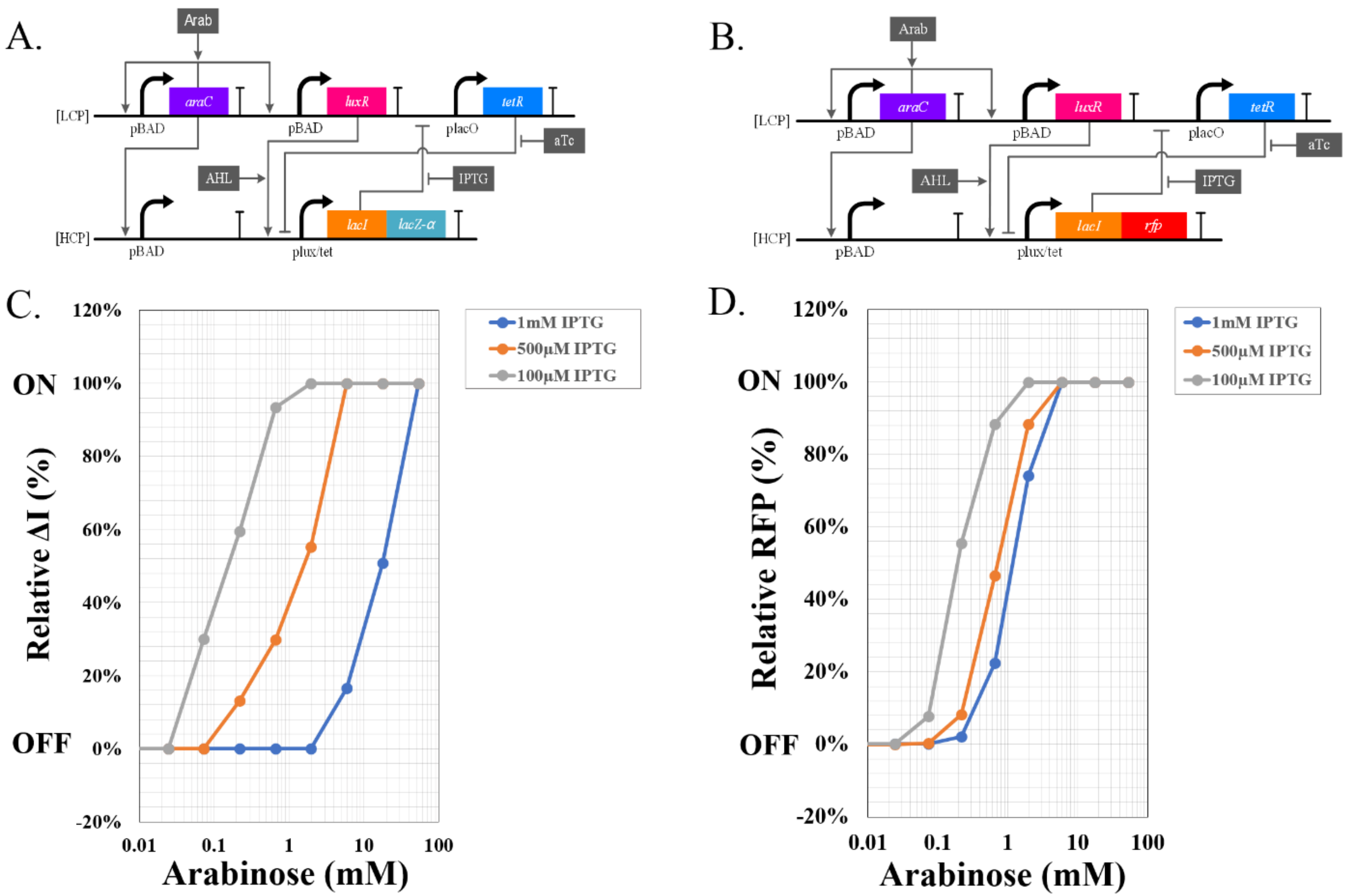
A Synthetic Biological Comparator [54]



(Zeng et al., NATURE Scientific Reports, 2019)

Bioelectronic Reporter system tested with the Synthetic Biological Comparator [54]

Electric reporting system | **Optical system**



(Zeng et al., NATURE Scientific Reports, 2019)

References

1. R. Sarpeshkar. *Ultra Low Power Bioelectronics: Fundamentals, Biomedical Applications, and Bio-Inspired Systems.* Cambridge University Press, Cambridge, UK, February 2010.
2. R. Sarpeshkar, "Analog Synthetic Biology", *Philosophical Transactions of the Royal Society, A*372:20130110, 2014.
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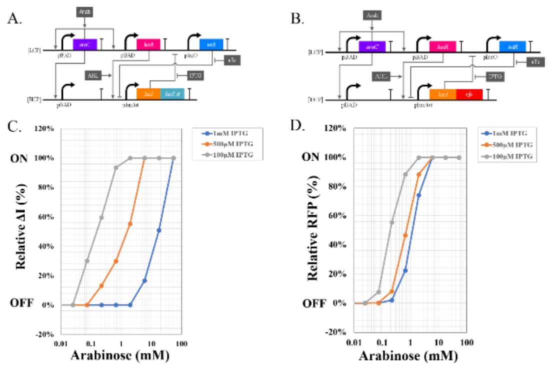
Energy, Information, and Power in Cells



Problem / Objective

(1) Identify 10+ Universal Principles for Bio-inspired Ultra-Energy-Efficient Information Processing from Molecule to Brain;(2) Measure Power-Speed-Precision and Energy-Information Tradeoffs in Microbial Cells. (3) Measure and Quantify the first ATP Atlas Of the Cell.

Technical Approach

Creation of Synthetic Microbial Circuits with Sensitive Electrical Reporting and Feedback; Measurement of ATP in Cells; Measurement of Power, Speed, and Precision in Cells; Circuit Modeling of Molecular Pathways in Cells

Uniqueness

- Energy-Efficient Synthetic Circuits in Cells; Controlled Probiotics for adaptive and intelligent medicine**;** Metabolic Engineering.
- Human-Performance Enhancers via ATP-based Molecular Insights; Universal Energy-Efficient Design Principles from Molecule to Insect/UAV Flight.

Description of Research

1. Developed a sensitive all-electrical molecular reporting system in living cells, useful for quantifying the costs of information and power in synthetic and natural cellular circuits; 2. Developed an ATP reporter system in cells that monitors ATP levels in cells in real time, which is useful for making all synthetic-biological circuits adapt to metabolic burden and relate energy, information, and power through fundamental quantitative relationships; 3. Developed circuits to model quantitative relationships between nutrients, metabolism, and ATP in cells; 4. Showed how analog circuits can help design sophisticated cell-population and cell-type control feedback systems; 5. Showed how the design of novel Bio-OpAmps and other synthetic biological circuits can be automated in the future with cytomorphic silicon chips.

Accomplishments

- **Publications:** 1) J. Zeng, A. Banerjee, J. Kim, Y. Deng, T. Chapman, R. Danial, and R. Sarpeshkar, “A Novel Bio-electronic Reporter System in Living Cells Tested with a Synthetic Biological Comparator”, NATURE Scientific Reports, doi:10.1038/s41598-019-43771. 2) J. Teo, R. Weiss, and R. Sarpeshkar, “An Artificial Tissue Homeostasis Circuit Designed via Analog Circuit Techniques”, *IEEE Trans. on Biomed. Circs. And Systems,* Vol. 13, No. 3, June 2019.
- **Presentations:** Design and Rapid Emulation of a Synthetic Microbial Operational Amplifier on Cytomorphic Silicon Chips, J. Teo, J. Zeng, S. Woo, and R. Sarpeshkar, Synthetic Biology: Engineering, Evolution, Design, NYC, June 2019.

Peers and Collaborators

- R. Weiss; R. Danial