Chemical Transistor Motif

Introduction

Systematically implementing biochemical control loops is a key aim in synthetic biology.[1] This would allow complex circuit functions to be built.Cellular functions like information processing,organization of metabolism, mechanical structure etc., are all fundamentally implemented by the proper "wiring" of protein reaction networks. Gene-regulatory networks arise at a higher level of system organization and the workings of chemical circuits are most fundamentally seen at the protein reaction level.[2]
Designing a protein reaction motif to achieve a specified form of dynamics has similarities to designing analog circuits.Both involve the control of flows (currents) and accumulations (voltages) of "charge"(electrons/chemical species) to achieve signal processing.[3]

Molecular "Currents" and Concentration "Voltages"

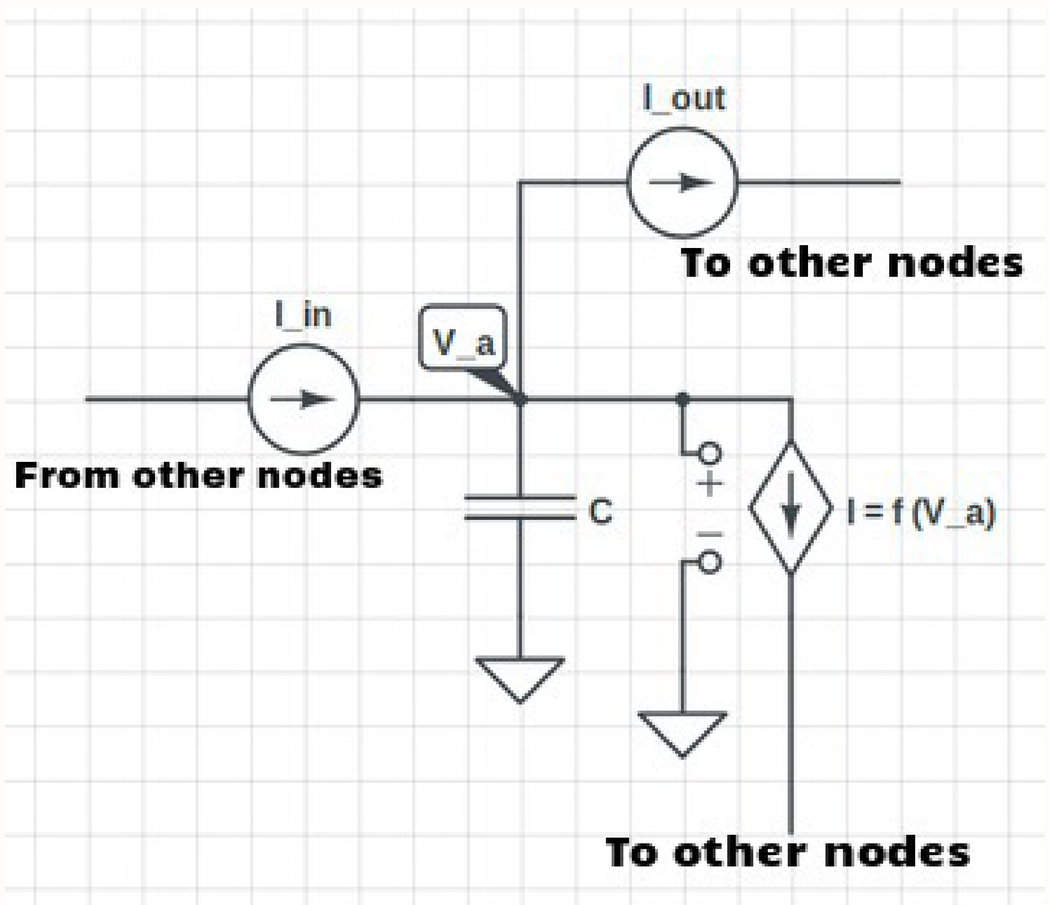

Figure 1: Electrical Circuit Node

$$\mathrm{I_{in}} = \mathrm{f}(V_A, other\ voltages) + \mathrm{I_{out}} + \mathrm{C}\frac{\mathrm{d}V_A}{\mathrm{dt}} \tag{1}$$

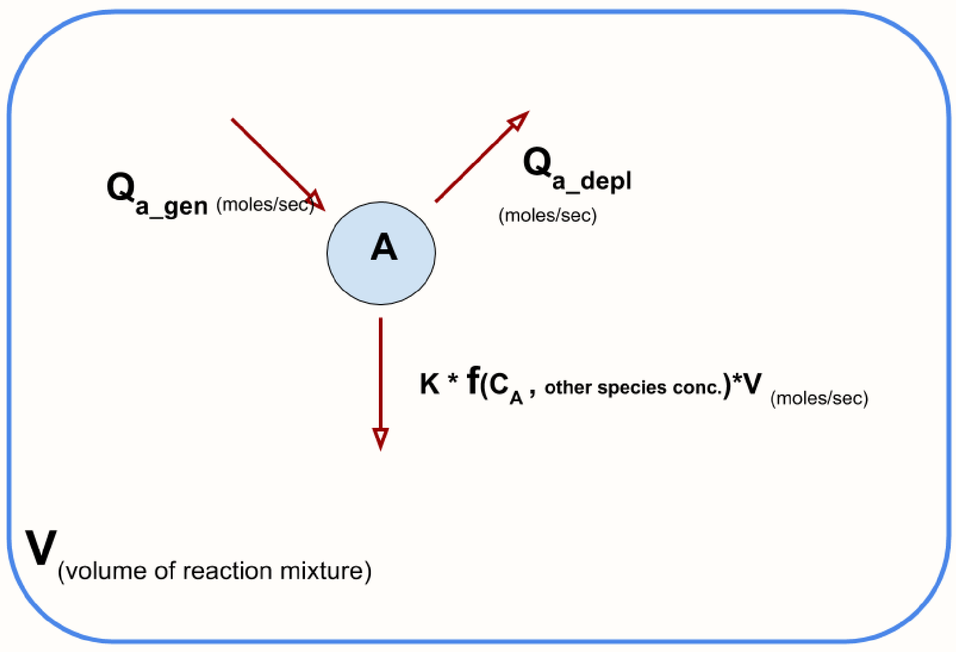

Figure 2: Chemical Species as a Circuit Node

$$\begin{gathered} Generation\ =\ Depletion\ by\ this\ reaction + \\ Depletion\ due\ to\ other\ reactions\ +\ Accumulation \end{gathered}$$

$$\mathrm{Q_{gen}}\ = \mathrm{k}\cdot\mathrm{f}(\mathrm{C_A}, other\ concentrations)V + \mathrm{Q_{depl}} + V\frac{\mathrm{dC_A}}{\mathrm{dt}} \tag{2}$$

Equation (1), charge conservation equation is analogous to Equation(2) mass balance. Dividing equation (2) by the Volume of the reaction mixture (V) results in an equation in terms of only intensive variables.Volumetric Generation/Depletion rate can be interpreted as a "current" entering/leaving the "node".Concentration of the species A at Chemical Node A [fig.(2)] is analogous to the Voltage of the Electrical Node A [fig.(1)].The reaction which is being separately represented in [fig.(2)] is analogous to a nonlinear voltage controlled current source in [fig.(1)]. The restriction on the analogy is that every electrical node must have an identical capacitor to the ground and the reaction volume,V,be fixed.

Implementing a Biochemical Transistor

The idea of the transistor has been implemented using technologies as different as vacuum tubes and solid state devices.Its extraordinary importance in circuit design is due to its following properties -

- Serves as a signal amplifier.
- The device is unilateral - 2 input nodes, 1 output node.
- It is the most elementary controlled source ("current valve") available as a single block for design.
- Enables implementation of both type of feedback loops. One node voltage actuates the output current positively,other node voltage actuates it negatively and the third node has no effect.
- Operates at 2 well separated time scales - DC Bias (Steady state), Small signal (Perturbations).The former is used to tune the latter.

I propose the following elementary interaction network which appears to share these above properties.The network is inspired from a sub-motif in the TOR signalling pathway of *S.cerevisiae*[4].

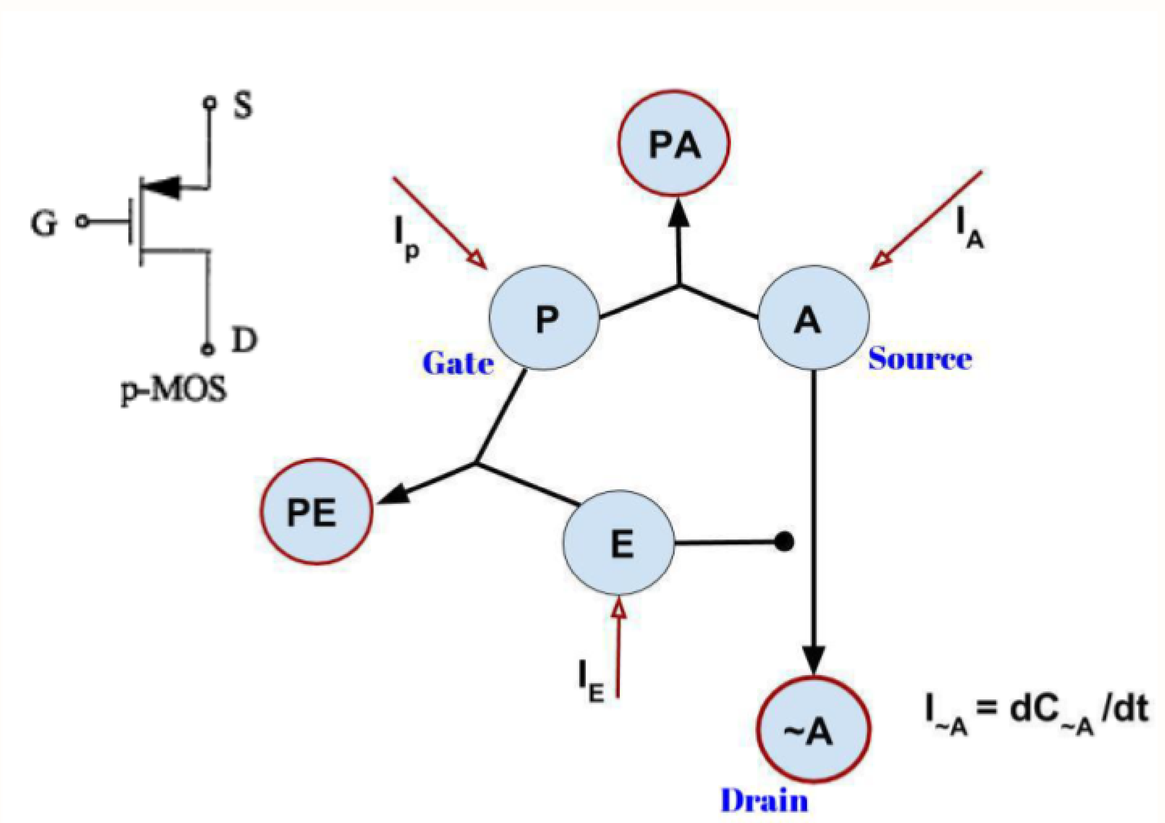

Figure 3: Proposed Motif: P associates with E and A : E is the enzyme

Similarities to P-MOSFET Action in Saturation

1. **Unilaterality**: AE(Enzyme-substrate complex) $\rightarrow$ A is extremely irreversible. Any imposed perturbation to $\mathrm{C_A}$ has no influence on the remaining network. A is an "Output node" - similar to the drain in common source PMOS transistor.
2. **BIAS**: Assume a constant molecular current goes into node P, node A and node E. Also assume the currents can be sourced from other reactions which generate these molecules. In steady state, PA , PE and A will be generated at a constant rate.This can be interpreted as an emerging current which may be routed to other reactions. In the absence of any further reactions downstream,these molecules would accumulate in the volume.In steady state, nodes P, A and E will settle to a constant concentration("Voltage"),while a constant "drain current" emerges from A.The network is thus "biased" to an "operating point".
3. **Gate Control**: P is the Gate, A is the Source, A is the drain. If a molecular current is pushed into node P, its concentration (Gate Voltage) increases. This increase will pull down the enzyme concentration $\mathrm{C_E}$. This decreases A -> A rate. (Source-Drain current.)
4. **Source Control**: If a molecular current is pushed into node A (Source), its concentration (Source Voltage) increases. This increase will pull down $\mathrm{C_P}$ in turn pushing up the enzyme concentration $\mathrm{C_E}$. This increases A -> A rate. (Source-Drain current.)
   This is particularly important as it implements negative feedback action - An increase in "Source Voltage"($\mathrm{C_A}$) causes a larger "Source-Drain Current" to be pulled out of that node thus pulling the "Source voltage" ($\mathrm{C_A}$) down.

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Modelling and Simulation

- A linearly increasing molecular current $i_p = 20\frac{\mu Moles}{sec^2} \cdot t$ was used to drive the circuit, i_a and i_e were held constant.
- $\frac{dC_A}{dt}$ ie., output current was obtained as a function of time.

The network was simulated in Python2.7.The source-code of the simulation is deposited in GitHub [5] for reference. All rate-constants were manually tuned using parameter sliders to adjust strengths of interactions.Other variables like initial conditions and currents held constant were also chosen similarly to obtain reasonable input to output gain. Output current vs input current is plotted below.

Result and discussions

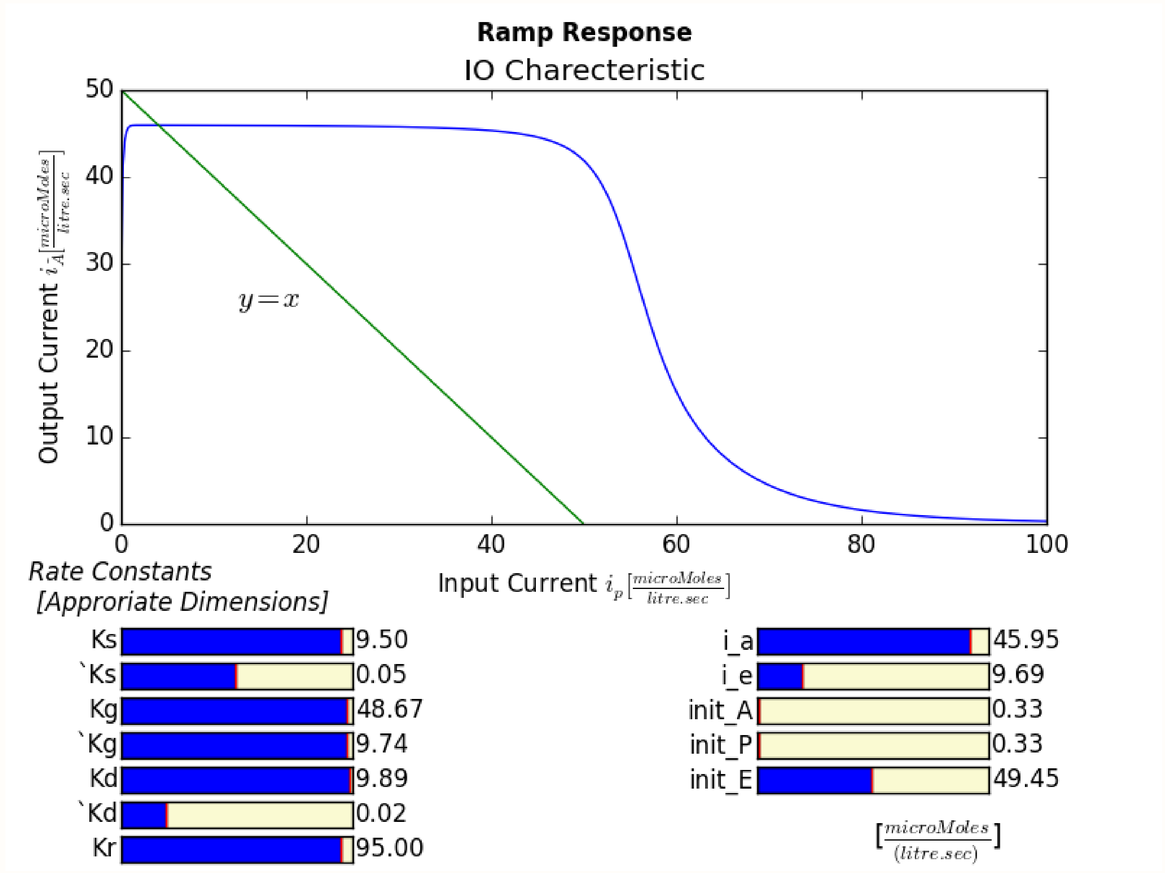

Figure 1: Output vs Input Current

Observation: For low values of input currents (i_p) the output current is nearly constant.
Explanation: With i_a in relative excess most of i_p is consumed by $P + A \rightarrow PA$ reaction thus it is unable to influence the enzyme levels.
Observation: At moderate input currents the output responds with a negative gain larger than 1.
Explanation: The enzyme levels come under the control of i_p causing an amplification.
Observation: At large i_p values output drops to zero and becomes insensitive to changes in input.
Explanation: At large i_p values material in i_a is routed into PA molecular current. Enzyme levels significantly drop thus throttling i_A.
Interestingly,the IO relationship is very similar to the IO relationship of a CMOS Inverter which is used as an amplifier when biased in the high gain region.

Summary and Further Directions

- Larger than unity gain seems to be achievable, but the nonlinear behaviour needs to be further scrutinized before attempting any design.
- Constant input currents used to "bias" the circuit may be sourced from other reactions whose dynamics are much slower than the one under consideration.
- The relevance of such an engineered network to real biological PPI networks needs to be further analyzed.Factors like feasibility of implementation and stochastic nature of the circuit needs to be analyzed.

If a reliable technique to achieve signal amplification in chemical circuits is designed, more complicated design problems like negative feedback control may be addressed in protein synthetic biology.Classical analog circuit design techniques would be indispensable.

References

[1] Del Vecchio, Domitilla, Aaron J. Dy, and Yili Qian. "Control Theory Meets Synthetic Biology." Journal of the Royal Society Interface 13.120 (2016): 20160380.

[2] Grünberg, Raik, and Luis Serrano. "Strategies for Protein Synthetic Biology." *Nucleic Acids Research* 38.8 (2010): 2663–2675.

[3] Teo JJY, Song SW, Sarpeshkar R. Synthetic biology: a unifying view and review using analog circuits. IEEE Trans Biomed Circ Syst. 2015; 9:453–74.

[4] Kuepfer L, Peter M, Sauer U, Stelling J. "Ensemble modeling for analysis of cell signaling dynamics." Nat Biotechnol. 2007;25(9):1001–1006. doi: 10.1038/nbt1330. pmid:17846631

[5] https://github.com/sooryasadayam/Mosfet-Motif.git

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