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Model Reference Circuits for Mitosis Control

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***Abstract*—After a review of different sets of equations covering mitosis we give a MATLAB realization of a basic set and from that we design some transistor circuits for their implementation. These can serve for a model reference for control of mitosis.**

I. Introduction

In order to stop the progression of cancer it should be important to stop uncontrolled cell division. This cell division occurs through the process of mitosis which is one stage in the cell cycle, the four main stages being shown in Figure 1. These stages are set out in standard texts [1] [2] and comprise the following:

1. Mitosis (M) when the cell divides in two
2. Gap one (G1) when proteins are assembled for DNA replication
3. DNA synthesis (S) when DNA is replicated
4. Gap two (G2) when the spindle for cell division is formed.

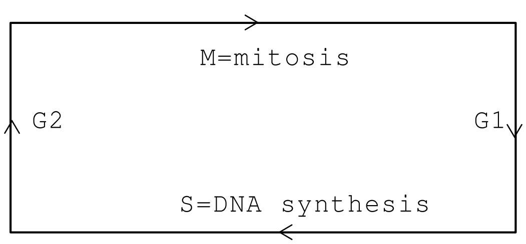

Figure 1. The four basic portions of the cell cycle

Although determination of all fine detail is still not complete, enough is known to be able to plot hundreds of molecular reactions [3]. And enough knowledge is available to be able to set up state variable equations which describe the primary activities of the cell. Indeed these exist in various levels of detail, almost all of which could be put into VLSI (Verry Large Scale Integrated) circuits but for which we concentrate upon a relatively simple set. For this we proceed by using the set of four state equations given by Petrov, Nikolova, and Timmer [4, p. 72] where the basic ideas follow those developed by Tyson and Novak [5]. One of the key notions of Tyson and Novak is that the S-G2-M-G1 cycle basically can be broken into two parts, the S-G2-M and the G1 portion, and, thus, their theory, which we follow here, is built around modeling signals representing these two portions of the full cycle.

Here we set up BJT (Bipolar Junction Transistor) circuits, suitable for VLSI fabrication, which realize a modified version of the equations of [4]. In the end these circuits can be used as model reference for control of mitosis for which almost any of the parameters can be used as inputs, including the cell mass, and for which outputs can be various molecules to control the mitosis.

II. The State Variable Equations

We follow the notation of [4] for the following four state variable equations.

$$\frac{dx}{dt} = k_1 - \left(k_2' + k_2'' y\right) x \qquad \text{(1a)}$$

$$\frac{dy}{dt} = \frac{\left(k_3' + k_3'' z\right)\left(1-y\right)}{j_3 + 1 - y} - \frac{k_4 m x y}{j_4 + y} \qquad \text{(1b)}$$

$$\frac{dz}{dt} = k_5' + k_5'' \frac{\left(mx\right)^n}{j_5^n + \left(mx\right)^n} - k_6 z \qquad \text{(1c)}$$

$$\frac{dm}{dt} = \mu m \left(1 - \frac{m z^p}{M}\right) \qquad \text{(1d)}$$

In these the state variables have physical meaning, these being given in Table 1

Table 1. Variables Definition		
x	:	Cyclin/Ckd dimmer concentration
y	:	Active Cdh1/APC complex concentration
z	:	Concentration of phosphatase Cdc14 that activates Cdh1 at end of mitosis
m	:	Cell mass

The k's are rate constants, the j's are Michaelis-Menton constants with n, M, μ, and p being constants which are found by curve fitting. The values used in [4] are given in the following table.

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Table 2 Constants for equations (1)			
$k_1 = 0.04$	$k_2' = 0.04$	$k_2'' = 1$	$k_3' = 1$
$k_3'' = 10$	$k_4 = 35$	$k_5' = 0.005$	$k_5'' = 0.2$
$k_6 = 0.1$	$j_3 = 0.04$	$j_4 = 0.04$	$j_5 = 0.3$
$\mu = 0.01$	$M = 10$	$n = 4$	$p = 100$

Equations (1) are due to Tyson and Novak [5] where rather than equation (1d) for the cell mass, the mz^p/M term was without the z^p; then m was scaled down to m/2 when it exceeded the maximum size, m*, to which a cell could grow with the value m*=1.2 chosen [5, p. 255]. Figure 2 shows typical solutions for x, y, z, and m of the mitosis equations of (1) as obtained from Simulink. Note that m does reset to about half when the division occurs and that there are two distinctive portions to the cycle.

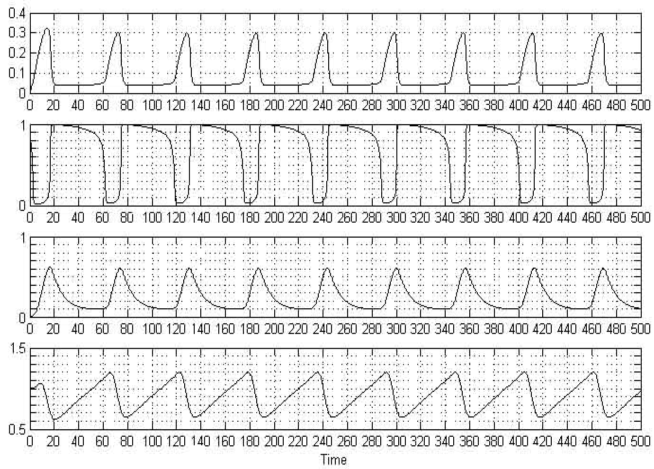

Figure 2 typical x, y, z, m signals from Simulink runs.

Since p=100 in equation (1d) is very inconvenient for transistor realization we have found that similar results occur when (1d) is replaced by

$$\frac{dm}{dt} = \mu m\left(1 - 10m\left(z-1\right)\right) \qquad (1e)$$

(where we have used the fact that $\mathrm{M} = 10$). Therefore for transistorization we use (1e) along with (1a)-(1c). In order to use BJT's or CMOS in subthreshold we desire exponential nonlinearities for which we make the following change of variables

$$x = e^{\alpha}, y = e^{\beta}, z = e^{\gamma}, m = e^{\delta} \qquad (2a,b,c,d)$$

Applying these to equations (1) gives

$$\frac{da}{dt} = k_1 e^{-\alpha} - k_2' - k_2'' e^{\beta} \qquad (3a)$$

$$\frac{d\beta}{dt} = \left(k_3' + k_3'' e^{\gamma} - \frac{j_3}{j_3 + 1 - e^{\beta}}\right)e^{-\beta} - \frac{k_4 e^{\alpha+\delta}}{j_4 + e^{\beta}} \qquad (3b)$$

$$\frac{d\gamma}{dt} = \left(k_5' + k_5'' - \frac{k_5'' j_5^n}{j_5^n + e^{n(a+\delta)}}\right)e^{-\gamma} - k_6 \qquad (3c)$$

$$\frac{d\delta}{dt} = \mu - \frac{\mu}{M} e^{\delta + p\gamma} \qquad (3d)$$

$$\frac{d\delta}{dt} = \mu\left(1 - 10e^{\delta+\gamma} + 10e^{\delta}\right) \qquad (3e)$$

III. TRANSLINEAR BJT CIRCUIT IMPLEMENTATION OF THE STATE VARIABLE EQUATIONS

Each of these equations is realized by Bipolar Junction Transistor (BJT) transistor circuits along with current sources to give the various constants and capacitors, one for each derivative. We use the BJT's simplified -yet very accurate for normal operation- equation

$$I_C = I_S e^{\frac{V_{\mathrm{BE}}}{V_T}} \qquad (4)$$

where I_C is the collector's current, V_{BE} is the base-emitter current, and parameters I_S and V_T: I_S is the saturation current (typical value is 10^{-14} Amperes) and V_T is the thermal voltage (typical value is 26mV at room temperature.)

Figures 3 through 8 show the (sub)circuits realizing the system of equations (3a-e). To simplify the schematics, the collector terminals of the BJTs that are shown open are assumed connected to the positive power supply, V_{dd} . Also, all diodes are assumed to be implemented using a BJT with the base connected to the collector. Finally, all BJTs (and diodes) have the same geometry and size.

In deriving the differential equations modeling the circuits' behavior, we ignore the base currents assuming that the current gain, beta, of the BJTs is sufficiently large, i.e. 100 or more, which is a common case in current technologies. This assumption is typical in dealing with translinear circuits.

The state voltages α, β, γ and δ are represented by voltages $V_\alpha, V_\beta, V_\gamma$ and V_δ respectively. Specifically, we assume the representation

$$\begin{aligned} V_\alpha &= V_T\left(\alpha + \alpha_0\right), \; V_\beta = V_T\left(\beta + \beta_0\right), \\ V_\gamma &= V_T\left(\gamma + \gamma_0\right), \; V_\delta = V_T\left(\delta + \delta_0\right) \end{aligned} \qquad (5)$$

where $\alpha_0, \beta_0, \gamma_0, \delta_0$ are appropriate constants to allow for scaling and balancing of the circuit parameters.

Finally, in this analysis of the circuits we deliberately avoid mentioning where we use the translinear principle [6], a standard tool for analyzing translinear circuits, in an effort to make the paper and presentation accessible to a broader audience.

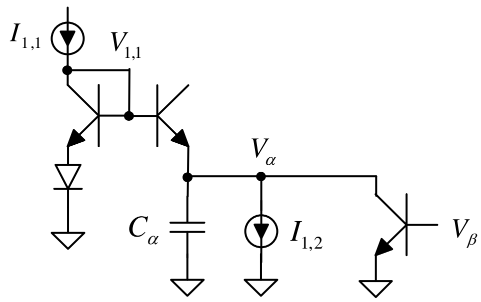

Figure 3, Subcircuit for the realization of Eq. (3a)

Figure 3 shows the subcircuit realizing Eq. (3a). Based on our assumptions above, we have $V_{1,1} = 2V_T \ln\left(I_{1,1}/I_S\right)$ as well as $C_\alpha \dfrac{dV_\alpha}{dt} = I_S e^{\frac{V_{1,1}-V_\alpha}{V_T}} - I_{1,2} - I_S e^{\frac{V_\beta}{V_T}}$.
Combining these two equations gives

$$C_\alpha \frac{dV_\alpha}{dt} = \frac{I_{1,1}^2}{I_S} e^{-\frac{V_\alpha}{V_T}} - I_{1,2} - I_S e^{\frac{V_\beta}{V_T}} \tag{6}$$

which matches Eq. (3a).

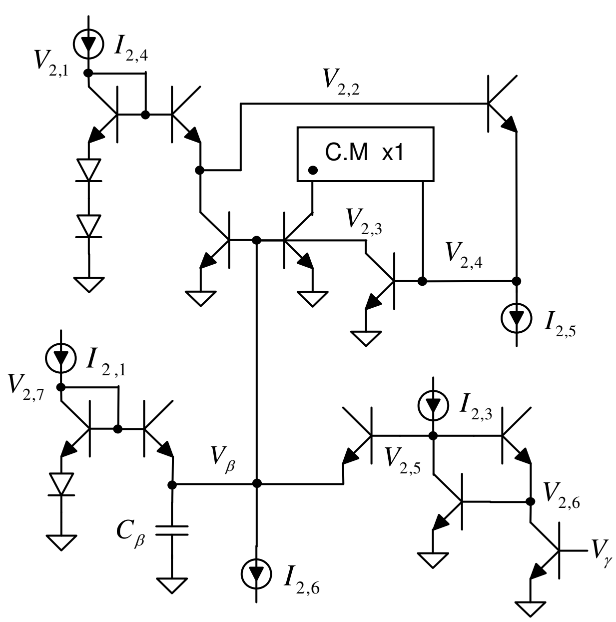

Figure 4, Subcircuit for the realization of Eq. (3b) - Part-1

The subcircuit in Figure 4 realizes differential equation (7). C.M. stands for "current mirror" [7].

$$C_\beta \frac{dV_\beta}{dt} = \frac{I_{2,1}{}^2}{I_S} e^{-\frac{V_\beta}{V_T}} + I_{2,3} e^{\frac{V_\gamma - V_\beta}{V_T}} - I_{2,6} - \frac{I_{2,4}^3 e^{-\frac{V_\beta}{V_T}}}{I_S \left(I_{2,5} - I_S e^{\frac{V_\beta}{V_T}}\right)} \tag{7}$$

where $I_{2,6}$ is derived using the subcircuit in Figure 5. To show this, we start from the top part of the circuit deriving $V_{2,1} = 3V_T \ln\left(I_{2,4}/I_s\right)$ exactly as in the previous subcircuit. Also, we have that $V_{2,2} = V_{2,1} - V_\beta$ as well as

$$V_{2,4} = V_{2,2} - V_T \ln\left(\frac{I_{2,5}}{I_S} - e^{\frac{V_\beta}{V_T}}\right)$$

giving

$$V_{2,4} = 3V_T \ln\left(\frac{I_{2,4}}{I_S}\right) - V_\beta - V_T \ln\left(\frac{I_{2,5}}{I_S} - e^{\frac{V_\beta}{V_T}}\right).$$

Moreover, from the bottom right part we have that $V_{2,5} = V_\gamma + V_T \ln\left(I_{2,3}/I_S\right)$. Finally from the bottom left part of the circuit we get

$$C_\beta \frac{dV_\beta}{dt} = \frac{I_{2,1}^2}{I_S} e^{-\frac{V_\beta}{V_T}} + I_S e^{\frac{V_{2,5}-V_\beta}{V_T}} - I_{2,6} - I_S e^{\frac{V_{2,4}}{V_T}} \tag{8}$$

which combined with the expressions for $V_{2,4}$ and $V_{2,5}$ results in Eq. (7). To match Eq. (7) to Eq. (3b) we generate current $I_{2,6}$ using the subcircuit in Fig. 5.

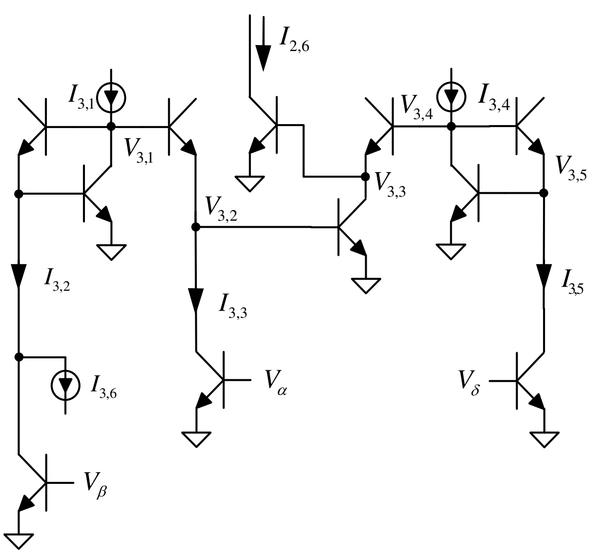

Figure 5, Subcircuit for the realization of Eq. (3b) - Part-2

Note that equations $V_{3,1} = V_T \ln\left(\dfrac{I_{3,1} I_{3,2}}{I_S^2}\right)$ and $V_{3,2} = V_{3,1} - V_T \ln\left(\dfrac{I_{3,3}}{I_S}\right)$ imply that

$V_{3,2} = V_T \ln\left(\frac{I_{3,1}I_{3,2}}{I_S I_{3,3}}\right)$. Also $V_{3,4} = V_T \ln\left(\frac{I_{3,4}I_{3,5}}{I_S^2}\right)$ as well as $V_{3,3} = V_{3,4} - V_{3,2}$. Combining these equations with $I_{3,2} = I_{3,6} + I_S e^{\frac{V_\beta}{V_T}}$, $I_{3,3} = I_S e^{\frac{V_\alpha}{V_T}}$ and $I_{3,5} = I_S e^{\frac{V_\delta}{V_T}}$ we get

$$I_{2,6} = I_S e^{\frac{V_{3,3}}{V_T}} = \frac{I_{3,4}I_{3,5}}{I_S} \cdot \frac{I_S I_{3,3}}{I_{3,1}I_{3,2}}$$

$$= \frac{I_{3,3}I_{3,4}I_{3,5}}{I_{3,1}I_{3,2}} = \frac{I_{3,4}I_S^2 e^{\frac{V_\alpha + V_\delta}{V_T}}}{I_{3,1}\left(I_{3,6} + I_S e^{\frac{V_\beta}{V_T}}\right)}$$

Which combined with (8) gives (7).

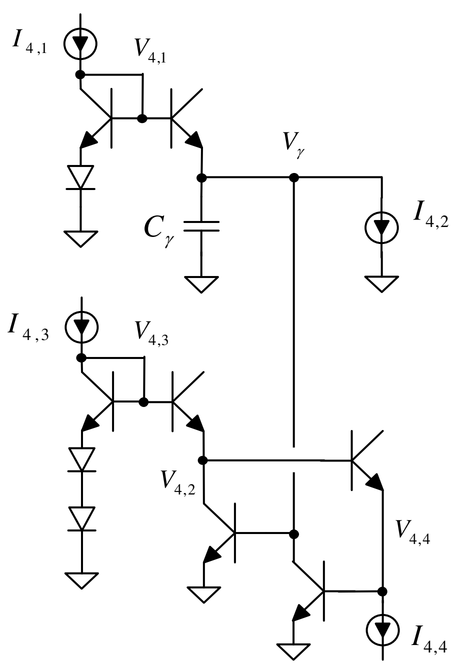

Figure 6, Subcircuit for the realization of Eq. (3c) - Part-1

The circuit in Figure 6 realizes Eq. (9)

$$C_\gamma \frac{dV_\gamma}{dt} = \frac{I_{4,1}^2}{I_S} e^{-\frac{V_\gamma}{V_T}} - I_{4,2} - \frac{I_{4,3}^3}{I_{4,4}I_S} e^{-\frac{V_\gamma}{V_T}} \qquad (9)$$

This can be verified starting from the top part of the circuit which gives

$$C_\gamma \frac{dV_\gamma}{dt} = \frac{I_{4,1}^2}{I_S} e^{-\frac{V_\gamma}{V_T}} - I_{4,2} - I_S e^{\frac{V_{4,4}}{V_T}}.$$

The bottom part of the circuit implies that

$$3V_T \ln\left(\frac{I_{4,3}}{I_S}\right) = V_{4,2} + V_\gamma$$

as well as

$$V_{4,2} = V_{4,4} + V_T \ln\left(\frac{I_{4,4}}{I_S}\right).$$

Combining the last three equations we get

$$V_{4,4} = 3V_T \ln\left(\frac{I_{4,3}}{I_S}\right) - V_\gamma - V_T \ln\left(\frac{I_{4,4}}{I_S}\right)$$
$$= V_T \ln\left(\frac{I_{4,3}^3}{I_S^2 I_{4,4}}\right) - V_\gamma$$

and Eq. (9). Current $I_{4,4}$ is generated by the following circuit.

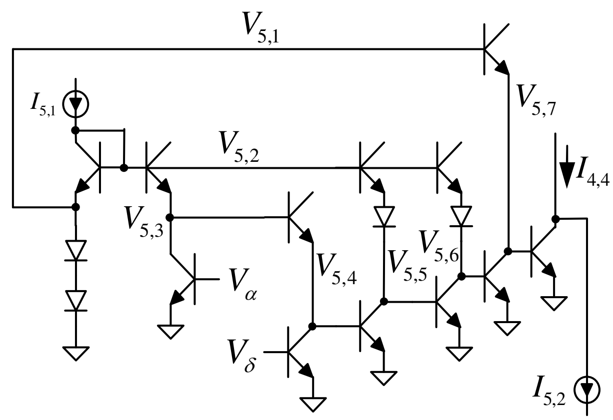

Figure 7, Subcircuit for the realization of Eq. (3c) - Part-2

It is $V_{5,2} = 3V_T \ln\left(\frac{I_{5,1}}{I_S}\right)$ and $V_{5,3} = 3V_T \ln\left(\frac{I_{5,1}}{I_S}\right) - V_a$ giving $V_{5,4} = 3V_T \ln\left(\frac{I_{5,1}}{I_S}\right) - V_a - V_\delta$, $V_{5,5} = V_{5,2} - 2V_{5,4}$, $V_{5,6} = V_{5,2} - 2V_{5,5}$ and $V_{5,7} = V_{5,1} - V_{5,6}$ where $V_{5,1}$ is given by $V_{5,1} = 2V_T \ln\left(\frac{I_{5,1}}{I_S}\right)$. Combining the above we get

$$V_{5,7} = V_{5,1} - V_{5,2} + 2V_{5,5}$$
$$= V_{5,1} + V_{5,2} - 4V_{5,4}$$
$$= 4\left(V_\alpha + V_\delta\right) - 7V_T \ln\left(\frac{I_{5,1}}{I_S}\right)$$

which implies that

$$I_{4,4} = I_S e^{\frac{V_{5,7}}{V_T}} + I_{5,2} = \frac{I_S^8}{I_{5,1}^7} e^{4\frac{V_\alpha + V_\delta}{V_T}} + I_{5,2} \quad (10)$$

Combining Eq. (9) with Eq. (10) gives

$$C_\gamma \frac{dV_\gamma}{dt} = \frac{I_{4,1}^2}{I_S} e^{-\frac{V_\gamma}{V_T}} - I_{4,2} - \frac{I_{4,3}^3 e^{-\frac{V_\gamma}{V_T}}}{I_S\left(\frac{I_S^8}{I_{5,1}^7} e^{4\frac{V_\alpha + V_\delta}{V_T}} + I_{5,2}\right)} \quad (11)$$

As seen here, we have selected to implement Eq. (3c) with $n = 4$ which is also listed in Table 2.

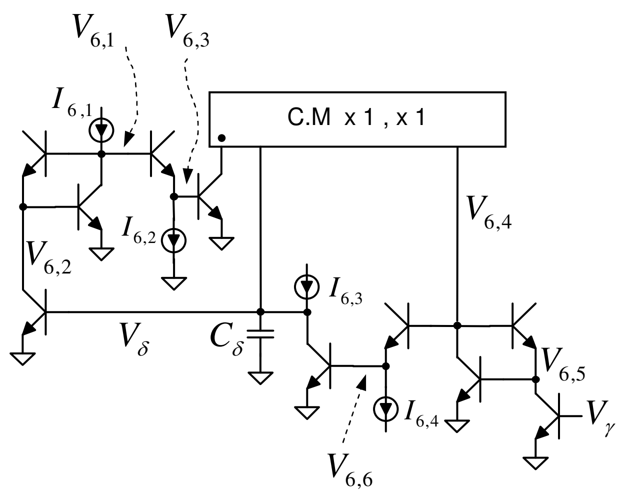

Figure 8, Subcircuit for the realization of Eq. (3e)

Finally, the last equation, (3e) is realized using the circuit in Figure 8 which gives $V_{6,1} = V_T \ln\left(\frac{I_{6,1}}{I_S}\right) + V_\delta$ and $V_{6,3} = V_{6,1} - V_T \ln\left(\frac{I_{6,2}}{I_S}\right)$ as well as $V_{6,4} = V_{6,3} + V_\gamma$, $V_{6,6} = V_{6,4} - V_T \ln\left(\frac{I_{6,4}}{I_S}\right)$ and the differential equation $C_\delta \frac{dV_\delta}{dt} = I_S e^{\frac{V_{6,3}}{V_T}} + I_{6,3} - I_S e^{\frac{V_{6,6}}{V_T}}$.

Combining the above gives $V_{6,3} = V_T \ln\left(\frac{I_{6,1}}{I_{6,2}}\right) + V_\delta$ and $V_{6,6} = V_T \ln\left(\frac{I_{6,1} I_S}{I_{6,2} I_{6,4}}\right) + V_\delta + V_\gamma$ resulting in

$$C_\delta \frac{dV_\delta}{dt} = \frac{I_{6,1} I_S}{I_{6,2}} e^{\frac{V_\delta}{V_T}} + I_{6,3} - \frac{I_{6,1} I_S^2}{I_{6,2} I_{6,4}} e^{\frac{V_\gamma + V_\delta}{V_T}}. \quad (12)$$

IV. Discussion

We have introduced the basics for realizing circuits which can serve as model references for control of mitosis. These are preliminary ones and due to limited space only a limited set of the circuits and simulation results are given. But this topic does give rise to a number of interesting areas where results are needed.

a) Sensors: In controlling mitosis it would be useful to be able to monitor the cell mass. But at present we are unaware of any sensors which would be suitable for doing this in real time non-invasively on a living body. One topic which may be suitable for investigation may be optical coherence tomography since it is being developed to "spot cancer at the smallest size" [8]

b) Circuits: The circuits given are just a start since the equations themselves are for the most primitive model available. Further the equations when converted to exponential form hold for both BJT (Bipolar Junction Transistors) and subthreshold operation of CMOS (Complementary Metal Oxide Silicon) transistors; further development could use either form. Since equation (1d) is empirical we have used an alternate in (1e) which gives equivalent responses (as found by trial and error) but which is more reasonable for transistor realization. We have found two others which are also convenient, these being

$$\frac{dm}{dt} = 0.2mz\left(1 - 0.35mz\right) \quad (1d')$$

$$\frac{dm}{dt} = 0.1m\left(1 - 10\left(\mathrm{sgn}(z-1)+1\right)\right) \quad (1d'')$$

Also there are polynomial forms of the basic equations and those are conveniently realized in standard analog CMOS form. These require various products as well as third and fourth order polynomials some of which we presently have under investigation.

c) Control: The original paper of Tyson and Novak [4] uses cell mass m as an "external" variable and it would seem that such may be the best variable to monitor for the control of cancer. In such a case m could be taken as the control system input. One also needs to determine reasonable outputs to feed to the cells. In [3] it is mentioned that any of the rate constants can be used as controls, but if truly rate constants they are constant. But the proteins and enzymes for which the rate constants apply can be changed in which case the determination of practical means of controlling them should be determined.

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