Piecewise linear map models for biological networks. The p53 example

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(work with C. Aguirre and J. Martins)
In modeling of biological processes, dynamical networks play an important role. Metabolic processes, Protein-protein, Gene expression and regulation, etc. A central role: oriented circuits or feedback loops [Snoussi & Thomas, 1993], [Thomas et al., 1995]. Positive or negative according to whether they have an even or odd number of negative interactions. General understanding: positive circuits generate multistability and negative circuits generate homeostasis [Snoussi, 1998], [Gouzé, 1998]. The difficult cases: positive and negative loops interacting and controlling each other.
In modeling of biological processes, dynamical networks play an important role.

- Metabolic processes, Protein-protein, Gene expression and regulation, etc.
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- The difficult cases: positive and negative loops interacting and controlling each other

**Modeling approaches:** (Thresholds and delays)
- Differential equations (with or without delays)
- The logic approach
- The piecewise linear approach
The acquired capabilities of cancer

- Self-sufficiency in growth signals
- Evading apoptosis
- Insensitivity to anti-growth signals
- Sustained angiogenesis
- Tissue invasion & metastasis
- Limitless replicative potential
The cell development circuitry
The p53 network

- p53 is a tumor suppressor gene. Its protein (transc. activ.) acts by:
  - Inhibition of progress through the cell cycle (p21, CDK’s,...)
  - Apoptosis (Bax, NOXA, ...)
  - Inhibition of blood-vessel formation (angiogenic phase)
  - Modulating the balance between respiration and glycolysis

- Is activated by:
  - DNA damage (ATM, Chk2)
  - Aberrant growth signals (p14ARF)
  - Cell stress (ATR, Casein II, ...)

- Is "off" in normal circumstances. Produced at some rate but degraded by ubiquitin labelling (MDM2, ...)

- Is activated through inhibition of degradation

- It activates its own controller

- In many tumors (~50%) it is found to be mutated

- In a number of cases normal p53 cannot achieve control
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In a number of cases normal p53 cannot achieve control
The p53 network
The "normal" inactivation of p53

<table>
<thead>
<tr>
<th>Mechanism of inactivating p53</th>
<th>Typical tumours</th>
<th>Effect of inactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino-acid-changing mutation in the DNA-binding domain</td>
<td>Colon, breast, lung, bladder, brain, pancreas, stomach, oesophagus and many others</td>
<td>Prevents p53 from binding to specific DNA sequences and activating the adjacent genes</td>
</tr>
<tr>
<td>Deletion of the carboxy-terminal domain</td>
<td>Occasional tumours at many different sites</td>
<td>Prevents the formation of tetramers of p53</td>
</tr>
<tr>
<td>Multiplication of the MDM2 gene in the genome</td>
<td>Sarcomas, brain</td>
<td>Extra MDM2 stimulates the degradation of p53</td>
</tr>
<tr>
<td>Viral infection</td>
<td>Cervix, liver, lymphomas</td>
<td>Products of viral oncogenes bind to and inactivate p53 in the cell, in some cases stimulating p53 degradation</td>
</tr>
<tr>
<td>Deletion of the p14&lt;sup&gt;ARF&lt;/sup&gt; gene</td>
<td>Breast, brain, lung and others, especially when p53 itself is not mutated</td>
<td>Failure to inhibit MDM2 and keep p53 degradation under control</td>
</tr>
<tr>
<td>Mislocalization of p53 to the cytoplasm, outside the nucleus</td>
<td>Breast, neuroblastomas</td>
<td>Lack of p53 function (p53 functions only in the nucleus)</td>
</tr>
</tbody>
</table>

The research motivation: Malfunction of wild type p53. (The other ~50% cases)
The complexity of gene expression regulation

- DNA → transcription
- RNA → translation
- protein → post-translational modification

- protein and modifier molecule

- transcripitional regulation
- translational regulation
- regulation of post-translational modification
The modular approach: Positive and negative circuits

Negative and positive circuits

1 — 2

1 2
The Thomas rules

- When a gene network has several non-degenerate steady states, the corresponding interaction graph has to contain, somewhere in the graph, a positive circuit. 
  **Positive circuit is necessary for multistability**

- When a gene network has oscillations, the corresponding interaction graph has to contain, somewhere in the graph, a negative circuit. 
  **Negative circuit is necessary for oscillations**
A model for the p53 network

Controlled positive and negative circuits in interaction
The equations: Piecewise linear maps

\[
\begin{align*}
p(t + 1) &= a_p p(t) + W_{pm} H(T_m - m(t)) \\
m(t + 1) &= a_m m(t) + W_{mp} H(p(t) - T_p) + W_{mg} H(T_g - g) \\
c(t + 1) &= a_c c(t) + W_{cb} H(b(t) - T_b) + W_{cp} H(T_p - p(t)) + W_{cg} H(g - T_g) \\
b(t + 1) &= a_b b(t) + W_{bc} H(c(t) - T_c) + W_{bp} H(T_p - p(t))
\end{align*}
\]

\(H\) is the Heaviside function, the \(T_i\)'s are the thresholds and in all cases

\[
a_i + \sum_k W_{ik} = 1
\]

\(W_{ik} > 0\). This condition insures that all intensities remain in interval \([0, 1]\).
The p-m system: a controlled negative circuit

\[ p(t + 1) = a_p p(t) + W_{pm} H(T_m - m(t)) \]

\[ m(t + 1) = a_m m(t) + W_{mp} H(p(t) - T_p) + W_{mg} H(T_g - g) \]
The p-m system: a controlled negative circuit

\[ f_{mp} = \frac{W_{mp}}{1 - a_m}; \quad f_{mg} = \frac{W_{mg}}{1 - a_m} \]
### The p-m system: a controlled negative circuit

<table>
<thead>
<tr>
<th>Condition</th>
<th>$g$</th>
<th>Asympt. behavior</th>
<th>Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_m &lt; fmg$</td>
<td>$g &lt; T_g$</td>
<td>$p \to 0, m \to fmg$</td>
<td>$0 \to 3 \to 1$</td>
</tr>
<tr>
<td>$T_m &gt; fmp$</td>
<td>$g &lt; T_g$</td>
<td>$p \to 0, m \to fmg$</td>
<td>$0 \to 3 \to 1$</td>
</tr>
<tr>
<td>$T_m &lt; fmg$</td>
<td>$g &gt; T_g$</td>
<td>$p \to 1, m \to fmg$</td>
<td>$1 \to 0 \to 2$</td>
</tr>
<tr>
<td>$T_m &lt; fmp$</td>
<td>$g &gt; T_g$</td>
<td>oscillation</td>
<td>$1 \to 0 \to 2$</td>
</tr>
<tr>
<td>$T_m &gt; fmg$</td>
<td>$g &lt; T_g$</td>
<td>oscillation</td>
<td>$1 \to 0 \to 2$</td>
</tr>
<tr>
<td>$T_m &gt; fmp$</td>
<td>$g &gt; T_g$</td>
<td>$p \to 1, m \to fmg$</td>
<td>$1 \to 0 \to 2$</td>
</tr>
<tr>
<td>$T_m &gt; fmg$</td>
<td>$g &lt; T_g$</td>
<td>oscillation</td>
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<td>$g &gt; T_g$</td>
<td>oscillation</td>
<td>$1 \to 0 \to 2$</td>
</tr>
</tbody>
</table>
The p-m system: a controlled negative circuit

- The period of the oscillations will depend on the values of the parameters, but the qualitative nature of the dynamics only depends on the relative positions of the thresholds and the quantities $fmg$ and $fmp$.

- Depending on the numerical values of the parameters, the system may stay for a number of time steps in each region but then it is forced to follow the arrows in the coding scheme.

- Of the above four working regimens, the first two ($T_m < fmg$) are the biologically relevant ones, because in the absence of oncogenes ($g$), normal p53 is expected to be at a low level. The other two regimens correspond to biologically detrimental action of this gene, provoking premature aging.

- Oscillations in the p53-MDM2 in response to a stress condition had been considered before [Bar-Or et al., 2000] [Brewer, 2002]. Our conclusion is that, in the biological normal region ($T_m < fmg$), a steady response is also possible if $T_m > fmp$. 
The c-b system: a doubly controlled positive circuit

\[ b(t+1) = a_b b(t) + W_{bc} H(c(t) - T_c) + W_{bp} H(T_p - p(t)) \]
\[ c(t+1) = a_c c(t) + W_{cb} H(b(t) - T_b) + W_{cp} H(T_p - p(t)) + W_{cg} H(g - T_g) \]

\[ fcp = \frac{W_{cp}}{1-a_c}; \quad fcb = \frac{W_{cb}}{1-a_c}; \quad fcg = \frac{W_{cg}}{1-a_c}; \quad (fcp + fcb + fcg = 1) \]
\[ fbc = \frac{W_{bc}}{1-a_b}; \quad fbp = \frac{W_{bp}}{1-a_b}; \quad (fbc + fbp = 1) \]
The c-b system: a doubly controlled positive circuit

\[
\begin{array}{c}
\begin{array}{c}
\frac{Wcp}{1-a_c} \\
1-a_c
\end{array} & Tc & \begin{array}{c}
\frac{Weg}{1-a_c} \\
1-a_c
\end{array}
\end{array}
\]

\[
\begin{array}{c}
\begin{array}{c}
\frac{Wbp}{1-a_b} \\
1-a_b
\end{array} & b & \begin{array}{c}
\frac{Wcg}{1-a_c} \\
1-a_c
\end{array} & c
\end{array}
\]

\[
\begin{array}{c}
\begin{array}{c}
\frac{Wbp}{1-a_b} \\
1-a_b
\end{array} & a & d & \begin{array}{c}
\frac{Wcg}{1-a_c} \\
1-a_c
\end{array}
\end{array}
\]

\[
\begin{array}{c}
\begin{array}{c}
\frac{Wbp}{1-a_b} \\
1-a_b
\end{array} & c
\end{array}
\]

\[
\begin{array}{c}
\begin{array}{c}
\frac{g<Tg}{p<Tp} \\
g>Tg & p<Tp
\end{array} \\
\frac{g<Tg}{p>Tp} \\
g>Tg & p>Tp
\end{array}
\]
The c-b system: a doubly controlled positive circuit

**TABLE 2A. (Case \( g < T_g \) and \( p < T_p \))**

<table>
<thead>
<tr>
<th>( g &lt; T_g ), ( p &lt; T_p )</th>
<th>Asympt. behavior</th>
<th>Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_c &lt; fcp ) \n( T_b &lt; fbp )</td>
<td>( b \rightarrow 1 ) \n( c \rightarrow fcp + fcb )</td>
<td>( a \rightarrow d \leftarrow b ) \n( \uparrow c )</td>
</tr>
<tr>
<td>( T_c &lt; fcp ) \n( T_b &gt; fbp )</td>
<td>( b \rightarrow 1 ) \n( c \rightarrow fcp + fcb )</td>
<td>( a \rightarrow b \rightarrow d ) \n( \uparrow c )</td>
</tr>
<tr>
<td>( fcp + fcb &gt; T_c &gt; fcp ) \n( T_b &lt; fbp )</td>
<td>( b \rightarrow 1 ) \n( c \rightarrow fcp + fcb )</td>
<td>( a \rightarrow c \rightarrow d ) \n( \uparrow b )</td>
</tr>
<tr>
<td>( fcp + fcb &gt; T_c &gt; fcp ) \n( T_b &gt; fbp )</td>
<td>( b \rightarrow 1, c \rightarrow fcp + fcb ) \n( \text{or} ) \n( b \rightarrow fbp, c \rightarrow fcp ) \n( \text{or} ) \n( \text{oscillation} )</td>
<td>( d \circ ) \n( a \circ ) \n( b \equiv c )</td>
</tr>
<tr>
<td>( T_c &gt; fcp + fcb ) \n( T_b &lt; fbp )</td>
<td>( b \rightarrow fbp ) \n( c \rightarrow fcp + fcb )</td>
<td>( a \rightarrow c \leftarrow b ) \n( \uparrow d )</td>
</tr>
<tr>
<td>( T_c &gt; fcp + fcb ) \n( T_b &gt; fbp )</td>
<td>( b \rightarrow fbp ) \n( c \rightarrow fcp )</td>
<td>( b \rightarrow c \rightarrow a ) \n( \uparrow d )</td>
</tr>
</tbody>
</table>
The c-b system: a doubly controlled positive circuit

TABLE 2B. (Case $g < T_g$ and $p > T_p$)

<table>
<thead>
<tr>
<th>$g &lt; T_g$, $p &gt; T_p$</th>
<th>Asympt. behavior</th>
<th>Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_c &lt; fcb$</td>
<td>$b \to 0$, $c \to 0$ or $b \to fbc$, $c \to fcb$ or oscillation</td>
<td>a○</td>
</tr>
<tr>
<td>$T_b &lt; fbc$</td>
<td></td>
<td>d○</td>
</tr>
<tr>
<td>$T_c &lt; fcb$</td>
<td>$b \to 0$, $c \to 0$</td>
<td>c→b→a \uparrow d</td>
</tr>
<tr>
<td>$T_b &gt; fbc$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_c &gt; fcb$</td>
<td>$b \to 0$, $c \to 0$</td>
<td>b→c→a \uparrow d</td>
</tr>
<tr>
<td>$T_b &lt; fbc$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_c &gt; fcb$</td>
<td>$b \to 0$, $c \to 0$</td>
<td>c→a←b \uparrow d</td>
</tr>
<tr>
<td>$T_b &gt; fbc$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The c-b system: a doubly controlled positive circuit

TABLE 2C. (Case $g > T_g$ and $p < T_p$)

<table>
<thead>
<tr>
<th>$g &gt; T_g$, $p &lt; T_p$</th>
<th>Asympt. behavior</th>
<th>Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_c &lt; fcg + fcp$</td>
<td>$b \rightarrow 1$</td>
<td>$c \rightarrow d \leftrightarrow b$</td>
</tr>
<tr>
<td>$T_b &lt; fbp$</td>
<td>$c \rightarrow 1$</td>
<td>$a \uparrow$</td>
</tr>
<tr>
<td>$T_c &lt; fcg + fcp$</td>
<td>$b \rightarrow 1$</td>
<td>$a \rightarrow b \rightarrow d$</td>
</tr>
<tr>
<td>$T_b &gt; fbp$</td>
<td>$c \rightarrow 1$</td>
<td>$a \uparrow \rightarrow c \rightarrow d$</td>
</tr>
<tr>
<td>$T_c &gt; fcg + fcp$</td>
<td>$b \rightarrow 1$</td>
<td>$a \uparrow \rightarrow b$</td>
</tr>
<tr>
<td>$T_b &lt; fbp$</td>
<td>$c \rightarrow 1$</td>
<td>$d$</td>
</tr>
<tr>
<td>$T_c &gt; fcg + fcp$</td>
<td>$b \rightarrow 1, c \rightarrow 1$</td>
<td></td>
</tr>
<tr>
<td>or $b \rightarrow fbp$, $c \rightarrow fcg + fcp$</td>
<td></td>
<td>$a$</td>
</tr>
<tr>
<td>or oscillation</td>
<td></td>
<td>$b \leftrightarrow c$</td>
</tr>
</tbody>
</table>
### TABLE 2D. (Case $g > T_g$ and $p > T_p$)

<table>
<thead>
<tr>
<th>$g &gt; T_g , p &gt; T_p$</th>
<th>Asympt. behavior</th>
<th>Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_c &lt; f_{cg}$</td>
<td>$b \rightarrow f_{bc}$</td>
<td>$a \rightarrow b \rightarrow d$</td>
</tr>
<tr>
<td>$T_b &lt; f_{bc}$</td>
<td>$c \rightarrow f_{cg} + f_{cb}$</td>
<td>$\uparrow c$</td>
</tr>
<tr>
<td>$T_c &lt; f_{cg}$</td>
<td>$b \rightarrow f_{bc}$</td>
<td>$a \rightarrow b \leftarrow d$</td>
</tr>
<tr>
<td>$T_b &gt; f_{bc}$</td>
<td>$c \rightarrow f_{cg}$</td>
<td>$\uparrow c$</td>
</tr>
<tr>
<td>$f_{cg} + f_{cb} &gt; T_c &gt; f_{cg}$</td>
<td>$b \rightarrow f_{bc}$, $c \rightarrow f_{cg} + f_{cb}$ or $b \rightarrow 0$, $c \rightarrow f_{cg}$ or oscillation</td>
<td>d○</td>
</tr>
<tr>
<td>$T_b &lt; f_{bc}$</td>
<td></td>
<td>a○</td>
</tr>
<tr>
<td>$f_{cg} + f_{cb} &gt; T_c &gt; f_{cg}$</td>
<td>$b \rightarrow 0$</td>
<td>bSa</td>
</tr>
<tr>
<td>$T_b &gt; f_{bc}$</td>
<td>$c \rightarrow f_{cg}$</td>
<td>c→b→a</td>
</tr>
<tr>
<td>$T_c &gt; f_{cg} + f_{cb}$</td>
<td>$b \rightarrow 0$</td>
<td>$\uparrow d$</td>
</tr>
<tr>
<td>$T_b &lt; f_{bc}$</td>
<td>$c \rightarrow f_{cg}$</td>
<td>b→c→a</td>
</tr>
<tr>
<td>$T_c &gt; f_{cg} + f_{cb}$</td>
<td>$b \rightarrow 0$</td>
<td>c→a→b</td>
</tr>
<tr>
<td>$T_b &gt; f_{bc}$</td>
<td>$c \rightarrow f_{cg}$</td>
<td>$\uparrow d$</td>
</tr>
</tbody>
</table>
Biological implications and the coupled system

- Biological parameter domain:
  - In the absence of cell abnormalities or oncogenes \((g < T_g)\), normal p53 will be at a low level.

\[ T_m < fmg \]

- On the absence of oncogenes and low p53, cell growth should not be explosive

\[ T_c > fcp + fcb \]
\[ T_b > fbp \]

then also \(T_c > fcb\).

- If \(g < T_g\) and \(p > T_p\), then \(b \to 0\) and \(c \to 0\). That is, in the absence of oncogenes, expression of p53 blocks cell growth.

- In all cases, when \(g > T_g\) (presence of oncogenes) and \(p < T_p\), there is explosive cell growth \((c \to 1)\). Only in the special case \(T_c > fcg + fcp\) and \(T_b > fbp\) there are other solutions, but even in this case \(c \to 1\) is a possible solution.
The most interesting situation for cancer control is to analyze the effect of expressed p53 \((p > T_p)\) in the presence of oncogenes \((g > T_g)\) - (Table 2D)

For \(T_c > fcg + fcb\) (and any \(T_b\)) p53 controls cell growth, keeping it at a low level \((c \rightarrow fcg)\). A large value of \(T_c\) relates to the effectiveness of cell growth to stimulate the an increased level of blood supply. The larger \(T_c\) the less effective is the stimulation signal.

For \(T_c\) values smaller than \(fcg + fcb\) the inhibitory effect of p53 may not be so effective. For \(fcg + fcb > T_c > fcg\) and \(T_b < fbc\) there are several solutions and the outcome will depend on the initial conditions. For \(T_c < fcg\) and \(T_b < fbc\) no control is possible.

For parameter values of \(T_m\) and \(T_p\) for which the \(p - m\) system is driven towards a fixed point, the behavior of the coupled system may be read directly from the \(c - b\) tables of the previous section and the conclusions are as listed above. For oscillatory conditions on the \(p - m\) system, the behavior is more complex and several different regimens may be accessed.
Biological implications and the coupled system

An example: \((T_m < fmg, T_c > fcp + fcb \text{ and } T_b > fbp)\).

The following figures show the dynamical evolution of the variables \(p, m, b, \text{ and } c\) for the parameter values

\[
fmg = 0.55, \ fbp = 0.4, \ fcb = 0.35, \ fcp = 0.2
\]

and

\[
T_p = 0.5, \ T_m = 0.5, \ T_c = 0.6, \ T_b = 0.5
\]

This corresponds to the situation

\[
T_m < fmg, \ T_m > fmp
\]

in the \(p - m\) system and

\[
fcg + fcb > T_c > fcg, \ T_b < fbc
\]

in the \(c - b\) system.

The parameter values are the same for both figures. One sees that depending on the initial conditions, in one case the p53 action keeps \(c\) at a low level and in the other it does not.
Biological implications and the coupled system

\[
\begin{align*}
\alpha(t) & = \frac{1}{1 + e^{-t}} \\
E(t) & = \frac{t}{1 + t^2} \\
\beta(t) & = \frac{1}{1 + e^{-t}} \\
\gamma(t) & = \frac{t}{1 + t^2}
\end{align*}
\]
Biological implications and the coupled system

The same parameters for the $c - b$ system, but $T_m = 0.4$, that is, $T_m < fmg$ and $T_m < fmp$. Oscillation in the $p - m$ system but the action on the $c - b$ system is similar and it again depends on the initial conditions.

![Graphs showing oscillation patterns with time for different systems and parameters.](image-url)
Conclusions

1 - A complete mathematical characterization of its dynamical solutions and how they depend on the parameter values (thresholds and couplings). Threshold positions corresponds to stimulation or inhibition of the mechanisms of gene expression. A guide for therapeutic action.

2 - There is a biologically reasonable region of parameters for which the successful action of $p$, as an inhibitor of cell growth, strongly depends on the initial conditions.

3 - In about half of human cancers p53 action is lost through mutation in the p53 gene. In many of the remaining tumors, the p53 gene is intact but it does not achieve the proper response. [Woods & Vousden, 2001]. Several mechanisms have been proposed to explain the loss of genetically normal p53 action: Abnormal conformation, targeting for degradation by viral proteins, defective localization to the nucleus, amplification of MDM2, loss of ability to inhibit MDM2 through proteins such as $p14^{ARF}$ or loss of kinases that phosphorylate MDM2 and p53.

4 - The model suggests there is a range of biological parameters for which there would be a purely dynamic explanation for the failure of p53.
A stochastic reformulation?

Gene expression is the result of a large number of discrete events
Therefore, gene expression is a stochastic process with random time intervals between the reactions.
Thresholds and delays are essential features in biological networks. A stochastic model should maintain thresholds and represent delays by a stochastic time. May be represented by density-dependent transition probabilities.

**The controlled p-m system**

\[
\begin{align*}
   p(t + \Delta t) &= a_p p(t) + W_{pm} H(T_m - m(t)) B_1 \\
   m(t + \Delta t) &= a_m m(t) + W_{mp} H(p(t) - T_p) B_2 \\
   &+ W_{mg} H(T_g - g) B_2
\end{align*}
\]

\[B_i = 1 \text{ with probability } p \text{ and } = 0 \text{ with probability } 1 - p \quad \langle \tau \rangle = \frac{\Delta t}{p}\]
References

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