COMPUTATIONAL & PROCESS SYSTEMS APPROACHES TO RESOLVING THE TGF-β PARADOX IN CANCER

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WHAT IS TRANSFORMING GROWTH FACTOR-\( \beta \)?

TGF-\( \beta \)

Receptors

Smad4

RSmad

Proliferation

Apoptosis

Differentiation

Motility

Adhesion

Angiogenesis

Immuno-surveillance

CANCER CELL
THE TGF-BETA PARADOX IN CANCER PROGRESSION*

Normal Epithelium

Changes in genetic & epigenetic context

Invasive Metastatic Cancer

Suppressor activities dominate

TGF-β responsiveness

TGF-β expression/activation

Pro-oncogenic activities dominate

Tumor Cell Autonomously
- Growth inhibition
- Apoptosis
- Genomic stability

Effects on tumor stroma
- Immunosuppression
- Angiogenesis

*Adapted from Roberts & Wakefield (2003) PNAS 100;8621-8623
**Problem Statement: The TGF-β Paradox**

- How can a single cytokine, TGF-β, switch roles from a tumor suppressor to a tumor promoter?

- Why is the amount of TGF-β unusually high in cancer tissues, given that TGF-β is supposed to be a tumor suppressor and growth inhibitor?
OUTLINE

I. Single Cell Modeling (TGF-β Signal Transduction)
   – Model Development, Validation and Analysis
   – Hypotheses on the dual role of TGF-β

II. Macroscopic Model (TGF-β mediated regulation of cell population)
   – Control System Block Diagram, Modeling and Analysis
   – Simulations: Potential resolution of TGF-β paradox

III. Conclusions
I. SINGLE CELL MODELING
The TGF-β Signal Transduction Model

* Chung et al. (2009) Biophys. J 96(5) 1733-1750
Quantitative Modeling and Analysis of the Transforming Growth Factor β Signaling Pathway

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ABSTRACT   Transforming growth factor β (TGF-β) signaling, which regulates multiple cellular processes including proliferation, apoptosis, and differentiation, plays an important but incompletely understood role in normal and cancerous tissues. For instance, although TGF-β functions as a tumor suppressor in the premalignant stages of tumorigenesis, paradoxically, it also seems to act as a tumor promoter in advanced cancer leading to metastasis. The mechanisms by which TGF-β elicits such diverse responses during cancer progression are still not entirely clear. As a first step toward understanding TGF-β signaling quantitatively, we have developed a comprehensive, dynamic model of the canonical TGF-β pathway via Smad transcription factors. By describing how an extracellular signal of the TGF-β ligand is sensed by receptors and transmitted into the nucleus through intracellular Smad proteins, the model provides quantitative insight into how TGF-β-induced responses are modulated and regulated. Subsequent model analysis shows that mechanisms associated with Smad activation by ligand-activated receptor, nuclear complex formation among Smad proteins, and inactivation of ligand-activated Smad (e.g., degradation, dephosphorylation) may be critical for regulating TGF-β-targeted functional responses. The model was also used to predict dynamic characteristics of the Smad-mediated pathway in abnormal cells, from which we generated four testable hypotheses regarding potential mechanisms by which TGF-β’s tumor-suppressive roles may appear to morph into tumor-promotion during cancer progression.
MODEL OVERVIEW

• **System of non-linear ordinary differential equations**
  – 17 state variables / 37 parameters

  ![Differential Equation Diagram](image)

  \[
  \frac{dx}{dt} = f(x, p, u)
  \]

  \[
  x(t_0) = x_0
  \]

  \[
  \hat{y} = h(x)
  \]

• **Parameter Estimation**
  – Step 1: Initial Rough Estimation
  – Step 2: Parameter Sensitivity Analysis
  – Step 3: Least Squares Fitting to Data
  – Step 4: Parameter Identifiability Test
  – Step 5: Identifiable Parameter Estimate Refinement
DATA FITTING

A: total nuclear p-Smad2*
B: total cytoplasmic p-Smad2#
C: total nuclear Smad2#
D: total cytoplasmic Smad2#
E: total nuclear Smad4#

*: Inman et al. (2002)
#: Pierreux et al. (2000)
**Model Validation**

- **Total cellular pSmad2**
  - Lo and Massague (1999)

- **Total cytoplasmic Smad4**
  - Pierreux et al. (2000)

- **pSmad/Smad (step input)**
  - Lin et al. (2006)

- **pSmad/Smad (pulse input)**
  - Lin et al. (2006)
**In-silico Mutation of TGF-β Receptors**

- **Aim**
  - To investigate system behavior under cancerous conditions

- **Specific investigations**
  - 10-fold decrease in the initial amount and production rates of TGF-β receptors (to mimic known characteristic of cancerous cells).

**In-silico Mutation of TGF-b Receptors**

- Reduction in receptors may induce 1) attenuated and 2) transient system responses.

TGF-β Dose-Dependent Response

- Cancer cells require more TGF-β than normal cells in order to elicit the same nuclear Smad-mediated activity.

Why is the amount of TGF-β unusually high in cancers, given that TGF-β can function as a tumor suppressor/growth inhibitor?
HYPOTHESIS: A TGF-β CONTROL SYSTEM

• Premise
  – To elicit the same nuclear Smad-mediated activity, cancer cells require *more* TGF-β than normal cells.

• Hypothesis
  – There exists a **cellular control system** that uses the tumor suppressor ligand, TGF-β, to achieve its objective of regulating cell growth.
  – This control system functions effectively in normal cells because they are responsive to the ligand.
  – With cancerous cells, the still-intact control system must secrete *more* TGF-β to achieve the level of tumor suppression attainable with normal, responsive cells.
  – Increased level of TGF-β is therefore a **consequence** of this acquired TGF-β resistance exhibited by cancer cells.
II. MACROSCOPIC MODEL OF TGF-β REGULATION OF CELL POPULATION (PROSTATE GLAND)
OVERVIEW

• **Primary Objectives**
  – To provide a quantitative explanation of the contradictory roles of TGF-β during cancer progression that is consistent with clinical observations
  – To answer the question: *Why is the amount of TGF-β unusually high in cancers, given that TGF-β can function as a tumor suppressor or growth inhibitor?*

• **Approach & Tools**
  – Mathematical Modeling and Analysis
    (within a *Process and Control System Theory* framework)

*Reference:*
Also In:
A Control of TGF-β Pathway

Seung-Wook Choi and Babatunde A. Ogunnaike

Abstract. Although as a tumor suppressor, TGF-β is paradoxically increased in cancer cells, the underlying mechanism is opposite of TGF-β is unchanged from cancer patients with suppressor. To provide quantitative insights, we have developed a model of TGF-β model yields as to propose a plausible explanation for the paradoxically increased level of TGF-β in β resistance), no observed correlation is consistent with the clinically transgene.
A control engineering approach to understanding the TGF-β paradox in cancer

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TGF-β, a key cytokine that regulates diverse cellular processes, including proliferation and apoptosis, appears to function paradoxically as a tumor suppressor in normal cells, and as a tumor promoter in cancer cells, but the mechanisms underlying such contradictory roles remain unknown. In particular, given that this cytokine is primarily a tumor suppressor, the conundrum of the unusually high level of TGF-β observed in the primary cancer tissue and blood samples of cancer patients with the worst prognosis, remains unresolved. To provide a quantitative explanation of these paradoxical observations, we present, from a control theory perspective, a mechanistic model of TGF-β-driven regulation of cell homeostasis. Analysis of the overall system model yields quantitative insight into how cell population is regulated, enabling us to propose a plausible explanation for the paradox: with the tumour suppressor role of TGF-β unchanged from normal to cancer cells, we demonstrate that the observed increased level of TGF-β is an effect of cancer cell phenotypic progression (specifically, acquired TGF-β resistance), not the cause. We are thus able to explain precisely why the clinically observed correlation between elevated TGF-β levels and poor prognosis is in fact consistent with TGF-β’s original (and unchanged) role as a tumour suppressor.

Keywords: TGF-β; cancer; control theory; tissue homeostasis
MACROSCOPIC SYSTEM DESCRIPTION

• **The “Process:”** Prostate Gland (epithelial and stromal compartments)

• **Development and maintenance of function:**
  – Androgens (testosterone and dihydrotestosterone) continuously stimulate proliferation of prostate cells; inhibit apoptosis of prostatic epithelial cell
  – Androgen action in the prostate:
    ❖ Mediated through different stroma cell-derived *growth factors*
    ❖ Most important: IGF, EGF, bFGF, and TGF-β;

• **In normal prostate cells**
  – TGF-β induces differentiation,
  – inhibits prostate epithelial cell proliferation.
TGF-β-MEDIATED SYSTEM REGULATION

• Cells undergoing unusual growth
  – break basement membrane, encounter stroma: ⇒ inflammation;

• In response
  – TGF-β produced locally in latent form in the stroma;
  – Bioavailability of active TGF-β regulated by subsequent multistep process of activation

*In early stages, sufficient to kill off the cells, repair the damage and promote normal healing*
CONTROL SYSTEM BLOCK DIAGRAM OF TGF-β-DRIVEN REGULATION OF CELL HOMEOSTASIS

Develop component model for each block
**CONTROLLED PROCESS:**

**CELL PROLIFERATION + DEATH**

- **Cell Population Dynamics**
  - Proliferation: \( p \)
  - Death: \( d \)

- **Model Equations**
  \[
  \frac{dX}{dt} = (p(GF, TGF\beta) - d(TGF\beta)) \cdot X
  \]
  \[
  p(GF, TGF\beta) = \frac{p_a \cdot GF^r}{p_a + GF^r} - \frac{p_v \cdot TGF\beta^m}{p_v + TGF\beta^m}
  \]
  \[
  d(TGF\beta) = d_1 + \frac{d_2 \cdot TGF\beta^n}{d_3 + TGF\beta^n}
  \]
CONTROLLER: TGF-β PRODUCER CELLS

**Controller Response Function**

\[ LLC(t) = \frac{K}{1 + e^{(C_a(C_b-X))}} \]

- **The Sources of TGF-β**
  - Bone-marrow stroma
  - Blood platelets
  - Various immune cells (e.g. macrophages, dendritic cells, T cells, B cells etc.)
**Actuator: TGF-beta Activation System**

- **Controller**: TGFβ Secreting Cells
- **Actuator**: TGFβ Activation System (ECM)
- **Sensor**: Growth Factors (Disturbance)
- **Controlled Process**: Total cell population (Controlled Output)
- **Integrins**
- **Proteases**
**Latent TGF-β activation**

Activation by integrin-mediated cell traction force (Wipff & Hinz, 2008)

Activation by proteolytic cleavage (e.g. MMPs) (Dijke & Arthur, 2007)
**Actuator: TGF-β Activation System**

- **Release of inactive TGF-β from the ECM**
  - Proteolysis (by proteases)
  - Cell traction force (by integrins)

- **Model Equations**

  \[
  \frac{dTGF\beta}{dt} = \frac{k_{cat1} \cdot P \cdot LLC}{K_{m1} + LLC} + \frac{k_{cat2} \cdot I \cdot LLC}{K_{m2} + LLC} - k_d \cdot TGF\beta
  \]

  \[
  P = k_p \cdot X + PRT_0
  \]

  \[
  I = k_I \cdot X
  \]
**PARAMETER ESTIMATION (AN ILLUSTRATION)**

Parameter: $p(GF)$

Experimental data by Deenick et al., 2003
## Model Parameters

<table>
<thead>
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<th>Parameter</th>
<th>Value</th>
<th>Parameter</th>
<th>Value</th>
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<td>$p_a$</td>
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<td>$C_b$</td>
<td>1.155e+5</td>
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<td>$p_b$</td>
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<td>$K_p$</td>
<td>1E-05 nM/cell</td>
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<td>$r$</td>
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<td>4.25 μM</td>
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<tr>
<td>$C_a$</td>
<td>-4e-5</td>
<td></td>
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**SENSITIVITY ANALYSIS**

- **Controlled Process**
  \[
  \frac{dX}{dt} = (p(GF, TGF\beta) - d(TGF\beta)) \cdot X \\
  p(GF, TGF\beta) = \frac{p_a \cdot GF^r}{p_a + GF^r} - \frac{p_2 \cdot TGF\beta_m}{p_3 + TGF\beta^n} \\
  d(TGF\beta) = d_1 + \frac{d_2 \cdot TGF\beta^n}{d_3^n + TGF\beta^n}
  \]

- **Controller/Sensor**
  \[
  LLC(t) = \frac{K}{1 + e^{(C_s(C_t - X))}}
  \]

- **Actuator**
  \[
  \frac{dTGF\beta}{dt} = k_{cat1} \cdot P \cdot LLC + k_{cat2} \cdot I \cdot LLC - k_d \cdot TGF\beta \\
  P = k_p \cdot X + PRT_0 \\
  I = k_i \cdot X
  \]

\[
\langle NSC_j \rangle = \left. \frac{1}{T} \int_0^T \theta_j \frac{\partial X(t, \theta)}{\partial \theta_j} dt \right|_{\theta^*}
\]

- **X**: Total cell number
- **\theta**: parameter
SIMULATIONS

• Normal Conditions
  – Step input 100 nm in GF, Nominal Controller
  – Effect of controller parameter, K, on normal response

• Pathological Conditions
  – Reduced sensitivity to TGF-β stimulation (an established characteristic of cancer cells)
  – Effected by reducing cytostatic and apopototic efficiency of TGF-β.
  – Achieved via parameters $p_2$ and $d_2$ respectively
    ❖ Range: 100% - 33.33% efficiency
    ❖ Physiologically: from fully functioning receptors to three-fold reduction in number of functional receptors.
THE RESPONSES OF NORMAL CELLS

Latent TGF-β

Active TGF-β Level (Manipulated Input)

Cell Proliferation/Death

Controlled Process

Integrins

Proteases

Growth Factors (Disturbance)

Total cell population (Controlled Output)

CONTROLLER

Latent TGF-β Level

ACTUATOR

TGFβ Secreting Cells

TGFβ Activation System (ECM)

SENSOR

CONTROLLED PROCESS

Latent TGF-β

Bioactive TGF-β

Growth factors

Total Cell population

Growth factors
**THE EFFECT OF CONTROLLER PARAMETER**

\[
LLC(t) = \frac{K}{1 + e^{(C_a (C_b - X))}}
\]

**Simulation:**
- Nominal \( K=20 \)
- High \( K=40 \)
- Low \( K=10 \)

**Implication:**
Abnormal alterations in immune cell physiology may affect tissue homeostasis significantly.

**Simulation Results:**
- Latent TGF-\( \beta \)
- Bioactive TGF-\( \beta \)
- Cell population

![Graphs of LLC, TGF-\( \beta \), and Cell population](image-url)
CANCER CELLS: REDUCED FUNCTIONAL TGF-β RECEPTOR LEVELS

- In many human cancers, abnormal alterations (e.g. mutation, deletion, downregulation) in the TGF-β receptors are frequently observed.

- Aberrant alterations in the functional TGF-β receptors lead to reduced responsiveness of the cells to TGF-β.

CANCER CELLS: REDUCED FUNCTIONAL TGF-BETA RECEPTOR LEVELS

- **Controlled Process**

\[
\frac{dX}{dt} = (p(GF, TGF\beta) - d(TGF\beta)) \cdot X
\]

\[
p(GF, TGF\beta) = \frac{p_a \cdot GF^r}{p_b + GF^r} - \frac{p_2^r \cdot TGF\beta^m}{p_3^m + TGF\beta^m}
\]

\[
d(TGF\beta) = d_1 + \frac{d_2^n \cdot TGF\beta^n}{d_3^n + TGF\beta^n}
\]

- \( p_2 \): sensitivity to the *anti-proliferative* effect of TGF-\( \beta \)
- \( d_2 \): sensitivity to the *pro-apoptotic* effect of TGF-\( \beta \)

- **Simulation of Cancer Cell Behavior**
  - Reduce \( p_2 \) & \( d_2 \) simultaneously 1.5, 2, & 3 fold, respectively.

**NORMAL VS CANCEROUS**

- **Cell population**
  - Normal (100%)
  - Premalignant 1 (66.7%)
  - Premalignant 2 (50%)
  - Malignant (33.3%)

- **Proteases**
  - Normal (100%)
  - Premalignant 1 (67%)
  - Premalignant 2 (50%)
  - Malignant (33%)

- **Inactive TGFβ**
  - Normal (100%)
  - Premalignant 1 (67%)
  - Premalignant 2 (50%)
  - Malignant (33%)

- **Bioactive TGFβ**
  - Normal (100%)
  - Premalignant 1 (67%)
  - Premalignant 2 (50%)
  - Malignant (33%)

**Implication:**
The elevated TGF-β level in late cancers is due to insensitivity of cancer cells to the anti-growth effect of TGF-β.
KEY OBSERVATION

• Under Normal Conditions
  – Controller regulates growth, inhibits proliferation effectively using tumor suppressor ligand, TGF-β

• Under Cancerous Conditions (TGF-β resistance)
  – Role of TGF-β unchanged;
  – Control system still intact;
  – But now secretes more of TGF-β in a futile attempt to achieve the level of tumor suppression attainable with normal, responsive cells.
Stability Analysis (1)

\[ \frac{dX}{dt} = \left( p(GF, TGF \beta) - d(TGF \beta) \right) \cdot X = F(X) \]

\[ \frac{\partial F}{\partial X} = p(TGF \beta(X_{ss})) - d(TGF \beta(X_{ss})) + X_{ss} \cdot \left( \frac{\partial p}{\partial X}_{ss} - \frac{\partial d}{\partial X}_{ss} \right) = X_{ss} \cdot \left( \frac{\partial p}{\partial X}_{ss} - \frac{\partial d}{\partial X}_{ss} \right) \]

\[ = X_{ss} \cdot \left( \frac{\partial p}{\partial TGF \beta} \frac{\partial TGF \beta}{\partial X}_{ss} - \frac{\partial d}{\partial TGF \beta} \frac{\partial TGF \beta}{\partial X}_{ss} \right) \]

\[ = -X_{ss} \cdot \left( \frac{p_2 p_3^m m TGF \beta_{ss}}{(p_3^m + TGF \beta_{ss})^2} + \frac{d_2^w d_3^n n TGF \beta_{ss}}{(d_3^n + TGF \beta_{ss})^2} \right) \cdot \frac{\partial TGF \beta}{\partial X}_{ss} < 0 \]

where, \[ \frac{\partial TGF \beta}{\partial X}_{ss} = \frac{1}{k_{\text{deg}}} \cdot \left( \frac{k_{\text{cat}1} k_p K}{K_m (1 + e^{C_a(C_b - X_{ss})})} + K \right) \]

\[ + \frac{k_{\text{cat}1} (k_p X_{ss} + PRT_0) K K_m_1 C_a e^{C_a(C_b - X_{ss})}}{\left( K_m_1 (1 + e^{C_a(C_b - X_{ss})}) + K \right)^2} \]

\[ + \frac{k_{\text{cat}2} k_j K}{K_m (1 + e^{C_a(C_b - X_{ss})})} + K \]

\[ + \frac{k_{\text{cat}2} k_p X_{ss} K K_m_2 C_a e^{C_a(C_b - X_{ss})}}{\left( K_m_2 (1 + e^{C_a(C_b - X_{ss})}) + K \right)^2} \]

\[ > 0 \]

\[ \rightarrow \] The steady state of the closed-loop cell population system is always stable under nominal conditions.
Q: Under what conditions does the closed-loop system become unstable?

\[
\lim_{TGF\beta \to \infty} G = \lim_{TGF\beta \to \infty} (p - d)
\]
\[
= \lim_{TGF\beta \to \infty} \left( A - \frac{p_2^v \cdot TGF\beta^m}{p_3^m + TGF\beta^m} - \frac{d_2^w \cdot TGF\beta^n}{d_3^n + TGF\beta^n} \right)
\]
\[
= A - \left( p_2^v + d_2^w \right)
\]

where, \( A = \frac{p_a \cdot GF^r}{p_b^r + GF^r} - d_1 \)

If \( \left( p_2^v + d_2^w \right) < A \)
\rightarrow structurally unstable
(i.e. unbounded growth)

otherwise, stable
(i.e. finite cell population)

• Implication:
Treatment approach should focus on re-sensitizing cancer cells to tumor suppressive effect of the TGF-β.
ANALOGY TO TEMPERATURE CONTROL

Exothermic reactor

Temperature

Coolant addition

Time

Time

Coolant addition

Exothermic reactor

Coolant addition

Temperature
ANALOGY TO TEMPERATURE CONTROL

Resistance to the effect of the coolant
SUMMARY

• **Cellular model** provides novel insight into the system behavior under normal and cancerous conditions.
  – Nuclear complex formation between pSmad2 and Smad4 important for the accumulation of pSmad complex in the nucleus.
  – Normal and cancerous cells show different dynamic characteristics in terms of signal intensity and duration.
  – *To elicit normal nuclear Smad-mediated activity, cancer cells require more TGF-β than normal cells.*
**Summary**

- **Cellular model** functions as a hypothesis generating tool for elucidating the dual role of TGF-β.
  - Growth-inhibitory genes may require a higher Smad-mediated transcriptional activity for their expression than pro-oncogenic and pro-metastatic genes.
  - There exists a cellular control system that uses the tumor suppressive TGF-β to achieve its objective of regulating cell growth.

- **Macroscopic Control System Model** provides insight into plausible mechanism for counterintuitive clinical observation.
CONCLUSIONS

• Implications of Control System Model Simulation Results
  – Clinical observation is consistent with TGF-β’s role as a tumor suppressor: its level should increase in an attempt to elicit normal responses from a tumor that is becoming increasingly resistant to the cytokine

• Consequences (for how TGF-β ligand and TGF-β receptors are used as therapeutic agents)
  – Current approach (targeting TGF-β ligand therapeutically) may have to be abandoned in favor of re-sensitizing the cells to the tumor suppressive effect of the TGF-β, similar to treatment for diabetes mediated by prolonged insulin-resistance
**FUTURE WORK**

- **Experimental validation I (In-Vitro)**
  - Use a series of prostate cancer cell lines to test the predictions of the control system model regarding the effectiveness of TGF-β mediated regulation of cell growth and proliferation

- **Experimental validation II**
  - In-Vivo Identification of functional “controller/sensor” system.
FUTURE WORK: EXPERIMENTAL VALIDATION

Experimental Design

growth factor

Normal (e.g. PrEC)

growth factor

Pre-malignant (e.g. BPH-1)

growth factor

Malignant (e.g. LNCaP)

TGFβ

TGFβ

TGFβ
FUTURE WORK: EXPERIMENTAL VALIDATION

Hypothesized Outcomes

Normal (e.g. PrEC)

Pre-malignant (e.g. BPH)

Malignant (e.g. LNCaP)
ACKNOWLEDGEMENTS

• Professors Cooper, Farach-Carson & Sikes

• Funding
  – Institute for Multiscale Modeling of Biological Interactions (IMMMB) funded by DOE
  – DOD grant PC050554
  – NIH/National Cancer Institute P01 CA098912
  – NIH INBRE P20RR016472
  – The University of Delaware Research Foundation
QUESTIONS?