

Design of a Compensator Network to Stabilize Chaotic Tumor Growth

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Abstract Tumorigenesis can be modeled as a system of chaotic, nonlinear differential equations. From the analysis of these equations in state space, a feedback compensator is designed to stabilize the system based on a desired response. The feedback array constants represent four transducer molecules which could be used for any tumor type that obeys the same dynamics as the model, reducing drug investment requirements for a wider range of cancer treatment.

Keywords Chaotic • Tumor • Stabilization • State-space

1 Introduction

Tumorigenesis has been shown in many cases to be modeled as a system of chaotic, nonlinear differential equations [1–5]. Ivancevic et al. [1], in particular, has shown a universal model based on a reaction-diffusion cancer growth model, expressed by:

$$\frac{\partial n}{\partial t} = d_n \nabla^2 - \rho \nabla \bullet (\eta \nabla f) \quad (1)$$

$$\frac{\partial f}{\partial t} = \alpha \eta (m - f) \quad (2)$$

$$\frac{\partial m}{\partial t} = d_m \nabla^2 m + \kappa n - \sigma m \quad (3)$$

$$\frac{\partial c}{\partial t} = d_c \nabla^2 c + \nu f - \omega n - \phi c \quad (4)$$

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Where n denotes the tumor cell density, f is the MM-concentration, m is the MDE-concentration, and c is the oxygen concentration. This model has been investigated previously by the author using simulations and Wolfram CDF to determine that low oxygen environments and high glucose conditions will slow down tumorigenesis [6]. Similar results have been confirmed by studying cancer chromosomal instability (CIN) [7]. The above model by Ivancevic will be simplified so as to allow useful parameters to be applied for analysis in state space. Using standard models of state-space control, the conversion of the equations above to the Laplace domain will be used to design a compensation network to modify pole placement for optimum stability.

Current approaches to cancer therapy involve the development of molecular inhibitors that target specific proteins that are considered essential to the operation of tumor growth. As this approach changes with the biochemical process associated with each tumor and tissue type, the number of inhibitors that are designed is proportional to the number of tumor and tissue types, which is inefficient considering the current expense of drug development. The approach outlined in this paper utilizes years of theory in state space control that has been shown to work across many dynamical systems with a common outcome—a simplified set of feedback constants to stabilize any system that is determined to be controllable. This process is scalable across many biochemical systems and is therefore more efficient than designing a unique inhibitor to block specific biochemical processes for each type of tumor. The end result is a reduced set of molecular transducers that will stabilize tumorigenesis in any tissue, which hypothetically covers the dynamics of the molecular process of all cancerous growth.

2 State Space Analysis

From the reaction-diffusion cancer growth model above, a simplified non-dimensional non-spatial derivative model was found. This model was further modified by adding four additional parameters (α , β , γ , δ) which represents tumor cell volume, glucose level, number of tumor cells, and diffusion saturation level from the surface, respectively:

$$\dot{\eta} = 0 \quad (5)$$

$$\dot{f} = \alpha \eta (m - f) \quad (6)$$

$$\dot{m} = \beta \kappa n + f (\gamma - c) - m \quad (7)$$

$$\dot{c} = \nu f m - \omega n - \delta \phi c \quad (8)$$

A state-space analysis of a system of interdependent equations can be shown to take the form [8]:

$$\dot{x} = Ax + Bu \quad (9)$$

Where x is the state vector $[n, f, m, c]$, \dot{x} is the time derivative of the state vector, A is the state-transition matrix, B is the input matrix and u is the input which in this case we establish as a step-input for an example. This will not change the characteristic equation or resulting pole placement for the un-driven system. The equations in (5–8) produce the state-transition matrix A as follows:

$$A = \begin{bmatrix} 0 & 0 & 0 & 0 \\ \alpha m & -\alpha \eta & \alpha \eta & 0 \\ \beta \kappa & \gamma - c & -1 & -f \\ -\omega & \nu m & \nu f & -\delta \phi \end{bmatrix} \quad (10)$$

The characteristic equation of the system is found from the determinant of $(sI - A)$, where I is the identity matrix and s is the Laplace variable:

$$\begin{aligned} |sI - A| &= s^4 + s^3 (1 + \delta \phi + \alpha \eta) \\ &\quad + s^2 (\delta \phi + \nu f^2 + \alpha \eta + \alpha \eta \delta \phi + \alpha \eta c - \alpha \eta \gamma) \\ &\quad + s (\alpha \eta \delta \phi + \alpha \eta \nu f^2 + \alpha \eta c \delta \phi - \alpha \eta \gamma \delta \phi + \alpha \eta \nu m f) \end{aligned} \quad (11)$$

This characteristic equation has roots that shows the placement of poles in the s -domain which corresponds to the stability of the system. The following typical values (also used for the paper in [6]) are used to calculate the coefficients of (11): $\eta = 50$, $\nu = 0.5$, $\phi = 0.025$, $\alpha = 0.06$, $\gamma = 26.5$, $\delta = 40$. From this, the characteristic equation in (11) is:

$$s^4 + 5s^3 + 130s^2 + 1251s$$

which has the roots of:

$$s = -8.07803, s = 0, s = 1.53902 \pm 12.34892i$$

With the last two roots of $s = 1.53902 \pm 12.34892i$ lying in the right-hand side of the s -plane, making the system unstable and oscillatory (Fig. 4). The phase-space plot of this system shown in Fig. 1 diagrams the instability and associated chaotic attractor for the values used in this example, which corresponds to a cell with high oxygen and glucose conditions [6].

For poles in the right-hand side of the s -plane, the system is unstable and corresponds to metastatic growth. In order to control the system, we want to design a compensator that will place the poles in the left hand side of the plane at $s \leq 0$ for stability.

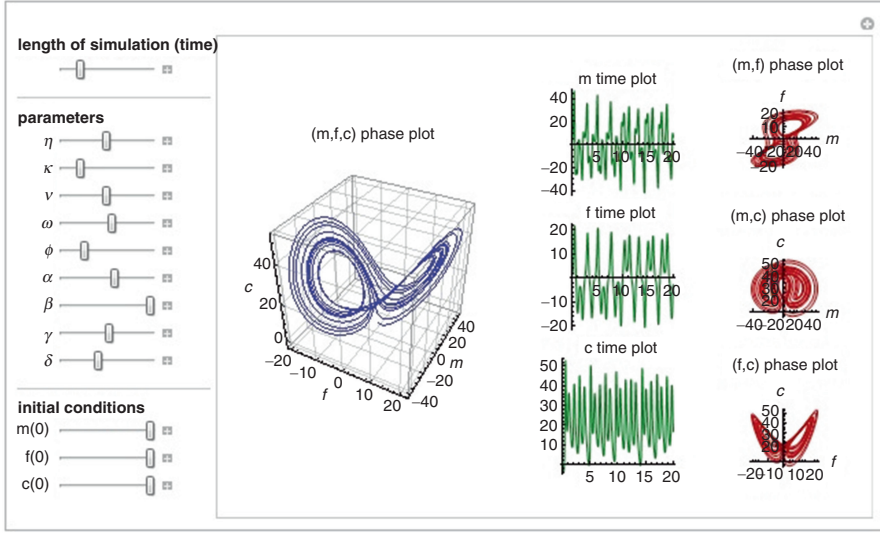


Fig. 1 State-space phase plot of unstable cellular growth, showing attractor

Fig. 2 State space control flow without compensator

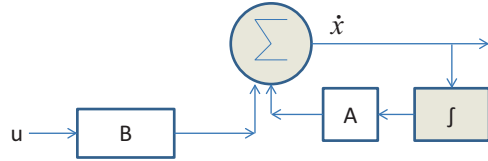
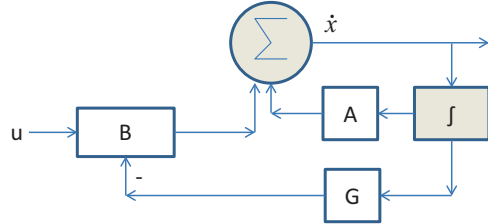


Fig. 3 State space control flow without compensator gain matrix G



3 Design of a Compensator

The open loop system for the state-space equations in (9–11) is shown in Fig. 2.

By adding a feedback loop to the input block B with gain coefficients for the output (shown in Fig. 3), a compensator is established which effectively changes the internal gain of the system and alters pole placement and therefore stability.

The determination of the G matrix is found by first determining the desired response based on the characteristic equation in (11). The equation in (11) is of the form:

$$s^4 + a_1s^3 + a_2s^2 + a_3s + a_4 \quad (12)$$

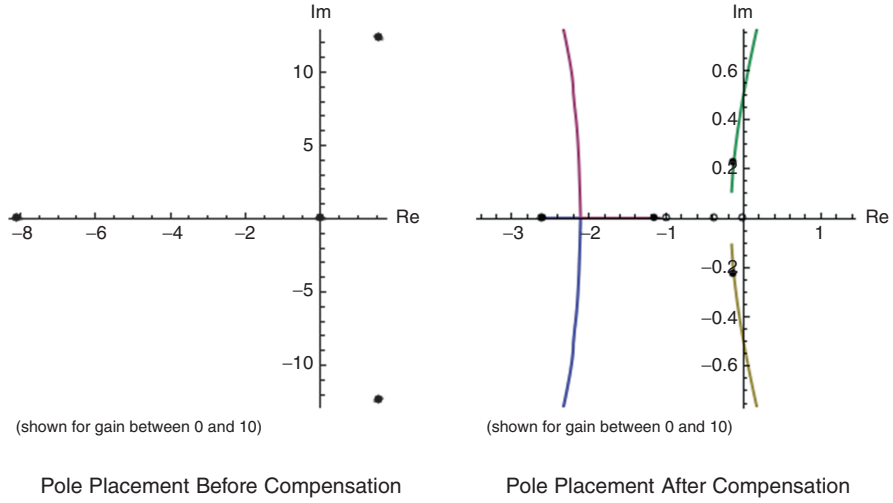


Fig. 4 Compensation moves poles to left-handed side of s-plane

Where a_1, a_2, a_3 and a_4 are the open-loop coefficients. Once the open-loop response is examined, the new coefficients are selected for the desired stability and these are represented by a_1', a_2', a_3' and a_4' for closed-loop response. For the example presented for (11), we had the values a_1, a_2, a_3 and a_4 given as (5, 130, 1251, 0) from the open-loop characteristic equation as $s^4 + 5s^3 + 130s^2 + 1251s$. The desired coefficients for stability (a_1', a_2', a_3' and a_4') may be set, for example, as (4, 4, 1, 0) which produces roots at $s = -0.38197, s = -2.6180, s = 0$ and $s = -1$. These roots are all on the left-hand side of the plane with no oscillatory response and are therefore stable (Fig. 4). The gain matrix is then found by equating the difference of the a vector with the a' vector:

$$G = [(QW)']^{-1} (a' - a) \quad (13)$$

Where Q is the controllability test matrix given by the concatenation of the input matrix B and the product of the input matrix with the state transition matrix AB where A and B are given in (9 and 10):

$$Q = [B, AB, A^2B, A^3B] \quad (14)$$

The matrix W in (13) is given by:

$$W = \begin{bmatrix} 1 & a_1 & a_2 & a_3 \\ 0 & 1 & a_1 & a_2 \\ 0 & 0 & 1 & a_1 \\ 0 & 0 & 0 & 1 \end{bmatrix} \quad (15)$$

Where a_1, a_2, a_3 are given in (12) and the product $[(QW)']^{-1}$ in (13) is the inverse of the transpose of the product of Q and W . The resulting gain matrix in (13) stabilizes the system by moving the poles to the left-hand side of the plane in comparison to the uncompensated system, which has poles in the right hand side of the plane (Fig. 4).

4 Interpretation of Results

The gain matrix as determined in (13) is a set of coefficients that represent the negative feedback of the state variables x , through transformation and scaling through the G matrix, for input into the system through the B matrix. As such, the G matrix represents transducer molecules that would interact with the known state variables (n as tumor cell density, f as the MM-concentration, m as the MDE-concentration, and c as the oxygen concentration) and produce an output at the same unit level as the input to the system u , in (9). If the initial model in (1–8) is correct, the design of these four transducer molecules to act as a feedback mechanism is all that is required to close the loop of tumorigenesis in order to stabilize tumor growth and reduce metastasis. If the model requires modification, then the requirements for the transducer molecules represented by the gain matrix in (13) changes with the new model. Whatever model is used, the hope is that it is accurate enough to model tumor behavior across many tissue domains, allowing for the treatment of a wide variety of cancers with only the same four molecular transducers. In contrast, current approaches to cancer therapy usually involve the development of molecular inhibitors that target specific proteins that are considered essential to the operation of tumor growth. As this approach changes with the biochemical process associated with each tumor and tissue type, the use of a standard control methodology such as this one that has been successfully tested for many decades on a variety of dynamical systems, offers a substantial improvement in the investment of drug development.

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