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Toward Genomic Based Personalized Mathematical Models for Breast Cancer Tumor Growth

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***Abstract*— Our *Genomic Relevance Parameterization* (GReP) model aims to explore a possible relationship between gene expression values from breast cancer patients and mathematical tumor growth modeling parameters calculated using data from clinical and preclinical measurements. We introduce two methods to relate genomic information and the tumor growth measurements. One method explores the impact of exponentiation of gene expression values, whereas the other utilizes the correlation between co-regulated genes and the growth parameters. As inputs to our GReP model, we used patient tumor volume measurements and genomic information for 74 breast cancer related genes from the I-SPY 1 TRIAL. We performed a preliminary validation of GReP model using experimental data from literature including MDA-MB-231 cell line, MDA-MB-231 cell line with CXCL12 gene over-expressed, and the MDA-MB-231 sub-cell lines 1834 and 4175. Tumor growth curves generated by GReP model, for the initial exponential phase of tumor growth closely match the pre-clinical data reported in the literature. These promising results show that it may be possible to build tools combining clinical information and genomic data to model cancerous tumor growth.**

***Index Terms*— tumor growth models, gene expressions, microarray data, breast cancer, I-SPY 1, exponential linear model.**

I. Introduction

Cancer behavior can be represented by signal pathway models [14], gene expression models [4], whole-cell models [15], and cell population models [13]. Pharmacokinetics (PK) and pharmacodynamics (PD) models focus on the absorbtion, distribution, metabolism, excretion from drugs, and the characteristics for the anti-cancer drugs on tumor cell death [9], [22].

Breast cancer is now considered five molecularly distinct neoplastic disorders [24]. Estrogen receptor ER status is a major factor to differentiate the expression phenotype for breast cancer [23]. Researchers describe breast cancer phenotypes for ER- and ER+ to be phenotypically very distinct groups [10], [26]. In this paper, we used the gene expressions and tumor size measurements from 79 breast cancer patients with ER+ status from I-SPY 1 TRIAL data.

In our previous work we evaluated treatments recommended by the *National Comprehensive Cancer Network* (NCCN) for HER2+ breast cancer [9] and ovarian cancer [28] in pre-clinical settings. We showed that the chemotherapy regimens recommended by the NCCN were effective in reducing tumor volume. In this paper, we introduce a model, called *Genomic Relevance Parameterization* (GReP) model, to explore a possible relationship between gene expression values from breast cancer patients and mathematical tumor growth modeling parameters calculated using clinical and preclinical measurements. We present two methods to build GReP model, one to investigate the impact of exponentiation of gene expression values, and the other to use correlation between co-regulated genes and the growth parameters.

As inputs to our GReP model, we used patient data made available by the I-SPY 1 TRIAL. It studied biomarkers with imaging for women with Stage-3 breast cancer [8], [7]. We used patient tumor volume measurements and genomic information for 74 breast cancer related genes for 79 patients.

Using the genomic data and MRI images from I-SPY 1 TRIAL as inputs for GReP model, we obtain a *Genomic Accordance Matrix* (GAM) to generate tumor growth parameters for an individual patient. A quantitative analysis was performed on the gene expression information and tumor volume measurements for mice with tumors derived from various cell lines reported in the literature (i.e., parental MDA-MB-231, and subpopulations 1834, 4175, and CXCL12 over-expressed) [2], [12], [20]. With this information, our GReP model generated tumor growth curves for these cell lines using exponentiation and correlation methods. Tumor growth curves generated by GReP model, for the initial phase of tumor growth, closely matches the pre-clinical data reported in the literature. These results encourage development of tools to discover the relationship between clinical information and genomic data for cancer patients.

II. Calculation of Tumor Growth Parameters

The relationship between genetic information and cancer has been studied in various contexts [25]. Pharmacogenomics combines the study of PK/PD models and genetics to relate gene expression to the metabolism, efficacy, and side effects of drugs [27]. PK and PD study the methods that the body absorbs drugs and their effects on the body, respectively. The goal of pharmacogenomics is to develop accurate models and translate them to clinical practice. We calculate tumor growth model parameters from clinical and preclinical data for breast and ovarian cancer patients [9], [28]. Our software tools use bio-inspired artificial intelligence methods developed at the earlier stages of our research [11], [17], [21].

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Typically in solid tumors, cells proliferate at an exponential rate during the early stages of the disease. The exponential-linear model [22], [16], [3] can characterize both the initial exponential growth phase and the consequent linear growth phase which occurs as the tumor begins to encounter space and nutrient limitations:

$$\begin{aligned} &\frac{dw(t)}{dt} = \lambda_0 \cdot w(t), && w(t) \leq w_{th} \\ &\frac{dw(t)}{dt} = \lambda_1, && w(t) > w_{th} \\ &w(0) = w_0 \end{aligned} \tag{1}$$

where $w(t)$ is the tumor weight at time t, and w_0 is the initial tumor weight. λ_0 and λ_1 are exponential and linear tumor growth parameters, respectively. Based on the tumor volumes obtained from MRI images, we compute the growth parameters of λ_0 and λ_1 in Eq.(1) for a set of ER+ patients.

For patients without MRI information, we can use the genetic information available in the database to approximate the parameters. The paired difference [5] of D_{p_1,p_2} between two sets of genetic information from patients p_1 and p_2 is:

$$D_{p_1,p_2} = \frac{1}{q \cdot r} \sum_{i=1}^{q} \sum_{j=1}^{r} |g_{i,p_1}^{j} - g_{i,p_2}^{j}| \tag{2}$$

where q is the number of selected breast cancer related genes, r is the highest order selected for gene expression values, and g_{i,p_1}^{j} and g_{i,p_2}^{j} are the j^{th} order of the i^{th} gene expression values for patients p_1 and p_2, respectively. For the patients without MRI, we identify the most genetically similar patient with MRI using the criteria in Eq.(2). Once a similar patient is identified, we calculate the tumor growth parameters of λ_0 and λ_1 within the range of $\pm 20\%$ of the original values.

III. GREP MODEL

We define a mathematical model, called *Genomic Relevance Parameterization* (GREP), to explore a possible relationship between gene expression values from breast cancer patients and mathematical tumor growth parameters calculated with the data from clinical and preclinical measurements.

For GREP model, λ_0 and λ_1 are calculated as in Sec. II. Next, using 74 genes relevant to breast cancer [19], [20], [26], we build a vector of gene expression values for ER+ patients. We then can calculate the coefficients of GREP model, representing the weight of each gene on the growth. In GREP, growth parameters are formulated as $K_{p_x} = < k_1, k_2, \cdots, k_\mu >$, which is a μ-dimensional vector for a patient p_x. When two tumor growth parameters are used, k_1 and k_2 correspond to λ_0 and λ_1, respectively. G_{p_x} is the m dimensional vector of the genetic information from patient x. The genetic data vectors for n patients constitute a genetic data matrix called $\mathfrak{G}$ of size $(m \times n)$. In GREP, the hypothesized relationship between tumor growth and genetic expressions is defined as:

$$K_{p_x} = \mathfrak{A} \cdot G_{p_x} \tag{3}$$

where $\mathfrak{A} = \left[a_{ij}\right]$ is called a Genomic Accordance Matrix (GAM) with the size of $(\mu \times m)$ for the number of tumor growth parameters of μ and the genetic data vector length of m. We developed two methods to relate tumor growth and genetic expressions by generating the genetic data vector G_{p_x}. Exponentiation of genomic expressions method applies multiple exponents to the expression value of each gene. Correlation of genomic expressions method builds G_{p_x} based on the correlation between co-regulated genes.

A. Exponentiation of Genomic Expressions

G_{p_x} can be derived using the genetic information for a patient. We exponentiate genomic expressions with multiple powers of each gene expression up to their r^{th} order:

$$G_{p_x} = < c,\ g_1,\ g_1^2, \cdots,\ g_1^r, \cdots,\ g_q,\ g_q^2, \cdots,\ g_q^r > \tag{4}$$

where q is the total number of genes and c is an offset. Genetic information may relate to tumor proliferation by a linear, square, or higher order function. To select the r value for GREP model we use bio-inspired computational techniques from our previous work [11], [17], [21].

In exponentiation of genomic expressions, the dimension of G_{p_x} vector is $(q \cdot r + 1)$ where q is the total number of genes included in the model. Since the size of each row in GAM (i.e., m) is equal to the size of the genetic data vector G_{p_x}, we have $m = q \cdot r + 1$. The exponentiated gene data vector (Eq.(4)) can be incorporated into GREP model (Eq.(3)) for the i^{th} tumor growth parameter of k_i as follows:

$$k_i = c \cdot a_{i,1} + \sum_{s=0}^{q-1} \sum_{t=1}^{r} a_{i,(s \cdot r + t + 1)} \cdot g_{(s+1)}^{t} \tag{5}$$

where $a_{i,j}$ is an element of GAM corresponding to the i^{th} tumor growth parameter and the j^{th} gene data vector parameter. The coefficient g_u^d is the u^{th} gene expression value of the patient and the d^{th} exponent of the vector.

B. Correlation of Genomic Expressions

For correlation between pairs of genes, we compute the Pearson correlation coefficients [18] for all possible pairs of genes using patient data from the I-SPY 1 TRIAL database [6].

Genetic data vector G_{p_x} is defined to identify the gene expression impact on tumor growth parameters. We take into account the pairwise interdependencies of genes on tumor growth by inclusion of new parameters calculated with a correlation function of gene arrays. We identify the correlated gene sets with parameter assignment function ζ_i:

$$\zeta_i = \prod_{j=1}^{|S_i|} g_{i,j} \tag{6}$$

where $g_{i,j}$ is the expression value of the j^{th} gene and $|S_i|$ is the total number of genes in subset S_i where $g_{i,j} \in S_i$. For correlated gene pairs, $|S_i| = 2$. With the computation of function ζ_v for all subsets, where v represents a subset, and including offset parameter c, vector G_{p_x} is:

$$G_{p_x} = < c,\ g_1, \cdots,\ g_q,\ \zeta_1, \cdots,\ \zeta_\kappa > \tag{7}$$

where integer q is defined as the total number of genes, and integer κ is the total number of correlated gene subsets. With correlation approach, the size of the genetic data vector for

each row of G_{p_x} is $m = q + \kappa + 1$. Using Eq. (3), the i^{th} tumor growth parameter k_i can be calculated:

$$k_i = c \cdot a_{i,1} + \sum_{s=1}^{q+\kappa} \begin{cases} a_{i,(s+1)} \cdot g_s & \text{if } s \leq q \\ a_{i,(s+1)} \cdot \zeta_{(s-q)} & \text{otherwise} \end{cases} \quad (8)$$

where $a_{i,j}$ is the j^{th} coefficient of the i^{th} row of $\mathfrak{A}$ matrix.

C. GAM calculation

The elements of $\mathfrak{A}$ matrix can be calculated using ER+ I-SPY 1 TRIAL patient genomic data and their tumor growth parameters as shown in Eq. (3). Let us define $\widetilde{K}^i$ as a vector which includes the different values for the i^{th} tumor growth parameter for all patients. $\widetilde{K}^i$ vector has n elements

$$\widetilde{K}^i = (\tilde{k}_{i,p_1}, \tilde{k}_{i,p_2}, \cdots, \tilde{k}_{i,p_n}) \quad (9)$$

where $\tilde{k}_{i,p_x}$ is the value of the i^{th} tumor growth parameter for patient x. $\widetilde{K}^i$ can be expressed with a set of equations:

$$\widetilde{K}^i = A^i \cdot \begin{bmatrix} C \\ G_R \end{bmatrix} \quad (10)$$

where A^i is the i^{th} row of $\mathfrak{A}$, G_R is the reduced form of matrix $\mathfrak{G}$ with dimensions of $(m-1) \times n$, and C is a single row consisting of n elements of the offset constant c. The coefficients in the i^{th} row of $\mathfrak{A}$ define a row vector as $A^i = (a_{i,1}, a_{i,2}, \cdots, a_{i,m})$ where $a_{i,j}$ is the j^{th} coefficient, corresponding to the i^{th} growth parameter for all patients. In Eq. (10), the reduced form of matrix $\mathfrak{G}$ is $G_R = \left[g_{ij}\right]$, where the constant coefficient c is excluded. Each vector A^i needs to be solved to calculate the tumor growth parameter k_i for patient x using Eqs. (5) and (8) for two methods.

IV. Quantitative Results

We analyze four case studies for our GREP model using existing data available in genetic and imaging databases. For each case, we generate a GAM matrix for the clinical data from 79 ER+ breast cancer patients in I-SPY 1 TRIAL. Specifically, we retrieve the genetic data from GEO database [6] and tumor growth parameters calculated from MRI information in NBIA database [1].

The experimental data used in the case studies are taken from several works presented in literature. Allinen et al. [2] reports tumor growth curves for MDA-MB-231 cell line and MDA-MB-231 cell line with CXCL12 gene over-expressed, which are used in case studies I (Sect. IV-A) and II (Sect. IV-B), respectively. For case studies III (Sect. IV-C) and IV (Sect. IV-D), the tumor growth information from Minn et al. [20] for the MDA-MB-231 sub-cell lines 1834 and 4175 are used, respectively. For genetic information, Minn et al. [20] studied 12 differentially expressed breast cancer related genes, whereas Ma et al. [19] provided top 50 genes differentially expressed in tumor epithelium for breast cancer. 70 prognostic marker genes for breast cancer are available in the study of Veer et al. [26]. Among all these genes, we retrieved 74 of them whose data is available in I-SPY 1 TRIAL for ER+ breast cancer patients. The selected genes for our study are shown in Table I.

MRI information at the initial diagnosis of cancer and immediately before treatment for each patient are available in I-SPY 1 TRIAL database. The measurements from these images are used to generate tumor growth parameters and curves. With tumor growth parameters computed, we can build GAM using the genetic information.

For case studies III and IV, growth parameters of λ_0 and λ_1 of the exponential-linear tumor growth model are computed using GAM and the genetic data vector G_{p_x} of patient x with Eqs. (3) and (5). But for case studies I and II, we only calculate λ_0 as the time period of exponential growth since the pre-clinical experiments were only conducted for 9 days (i.e., not enough time for λ_1). We used $c = 1$ and $r = 2$ for the exponentiation method.

TABLE I
74 GENES SELECTED FOR OUR ANALYSIS

AKAP2	DCK	GPM6B	MCM6	SCD
ANGPTL4	DHRS2	GSTM3	MELK	SERF1A
AP2B1	DMD	HIST1H1C	MMP1	SFRP1
BBC3	ECT2	HIST1H2BC	MMP9	SLC2A3
C10orf116	ELF5	HIST1H2BD	NAT1	SLC6A14
CCNE2	EMP1	HOXA9	NMU	SOSTDC1
CEACAM6	ESM1	ID4	PHLDA1	SPARCL1
CENPA	EXT1	IFI27	PRC1	TGFB3
CNTNAP2	FGF18	IFI6	PTGS2	WIF1
COL4A2	FLT1	IFIT1	RAB31	WISP1
CSF2RA	FOXC1	IGFBP5	RAB6B	
CX3CL1	FSCN1	KIAA1199	RARRES3	
CXCL1	GABRP	KIT	RFC4	
CXCL12	GMPS	KRT15	RGS2	
CYB561	GNAZ	LTBP1	RRM2	
CYP2B6	GPC1	MBNL2	S100P	

A. Case I: MDA-MB-231 Cell Line

The experimental data for this case study is taken from Allinen et al. [2], where they used cell-line MDA-MB-231. During their pre-clinical study, the tumor volume is measured throughout experiment of 9 days. These measurements (diamond shaped points in Fig. 1) illustrate that the tumor volume grows exponentially throughout the experiment.

From this experimental data, we calculate the tumor growth parameter of λ_0 and display the corresponding tumor growth in Fig. 1 as the square shaped points. With the gene expression values from the pre-clinical study by Minn et al.[20], we compute the value of λ_0 parameter using Eqs. (5) (exponentiation) and (8) (correlation). From Table II, the tumor growth curve generated by our GREP model closely matches with the curve from the experimental data. In Fig. 1, we present tumor growth curves for exponentiation and correlation methods with square and triangle shaped points, respectively. After the first five days of the experiment, the tumor growth from GREP model is slightly smaller than the experimental data for both methods. This encouraging results show that our GREP model can compute λ_0 value relatively accurately using individual patient gene expression values.

B. Case II: MDA-MB-231 - CXCL12 over-expressed

Figure 2 shows that the tumor growth from GREP model using both methods closely approximates the experimental data during the first days of the experiment. The values for

TABLE II

PARAMETER λ_0 FOR CASES I AND II

MDA-MB-231 cell lines			
Type	Experimental Data	GREP (Correlation)	GREP (Exponentiation)
MDA-MB-231	0.361	0.356	0.344
CXCL12	0.490	0.418	0.407

TABLE III

PARAMETERS λ_0 AND λ_1 FOR CASES III AND IV

Parameter	Experimental	GREP (Correlation)	GREP (Exponentiation)
MDA-MB-231 1834 sub-cell line			
λ_0	0.079	0.101	0.087
λ_1	22.180	33.188	37.934
MDA-MB-231 4175 sub-cell line			
λ_0	0.069	0.074	0.070
λ_1	38.560	22.151	47.468

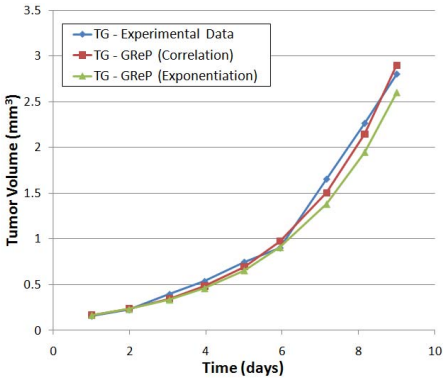

Fig. 1. Case I: Tumor growth from experimental data, and GREP model methods for MDA-MB-231 cell line

λ_0 for experimental data and for both GREP methods are in Table II. As the experiment progresses, the differences of the tumor volume becomes larger, starting at day 6. This divergence stems from the small disparity between the λ_0 values calculated by GREP and the λ_0 value corresponding to the experimental data as shown in Table II, resulting in tumor volumes with amplified differences over time.

C. Case III : MDA-MB-231 Sub-Cell Line 1834

The experimental data is taken from Minn et al. [20] for MDA-MB-231 sub-cell line 1834. During pre-clinical study the tumor size is measured for 48 days. In Fig. 3, the tumor grows exponentially for the first 39 days (in diamond shape), after which it grows linearly. The values for λ_0 and λ_1 corresponding to the experimental data are in Table III. GREP computes λ_0 and λ_1 values as given in Fig. 3 (triangle points for exponentiation and square points for correlation).

In Fig. 3, the measured and computed tumor volumes closely match for exponential growth. However, as the experiment advances, the difference between the tumor growth curves of experimental and the GREP model grows, similar to the observations from Case II.

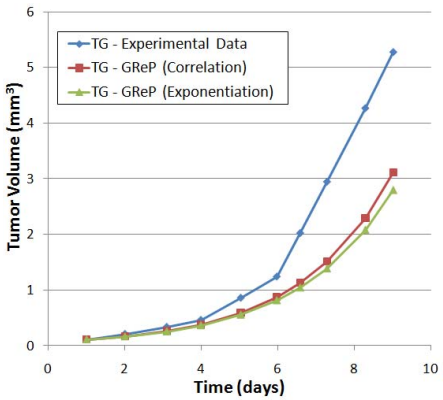

Fig. 2. Case II: Tumor growth from experimental data, and GREP model methods for MDA-MB-231 cell line with CXCL12 gene over-expressed

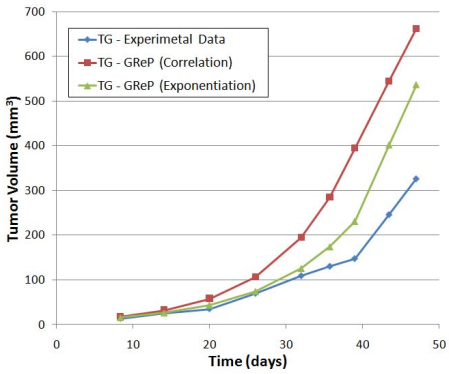

Fig. 3. Case III: Tumor growth results from experimental data, and GREP model methods for MDA-MB-231 cell line with sub-cell line 1834

D. Case IV: MDA-MB-231 Sub-Cell Line 4175

This case focuses on MDA-MB-231 sub-cell line 4175. Figure 4 shows the tumor volume from the experimental data and our GREP model for both methods. The initial tumor volume grows exponentially for the first 39 days after which becomes and stays linear until the end.We can observe in Fig. 4 that tumor growth generated by GREP model with both methods is close to the experimental data, especially at the first 38 days (Table III).

V. CONCLUDING REMARKS

In this paper we present our *Genomic Relevance Parameterization* (GREP) model to compute parameters for a mathematical breast cancer tumor growth model. We introduce two methods to investigate the possible relationship between genomic information and the tumor growth measurements. One method explores the impact of exponentiation of gene expression values, whereas the other utilizes the correlation between co-regulated genes and the growth parameters. As inputs to our GREP model, we used patient tumor volume measurements and genomic information for 74 breast cancer related genes from the I-SPY 1 TRIAL data set.

For preliminary validation of GREP model results, we used the data from several works presented in literature for pre-

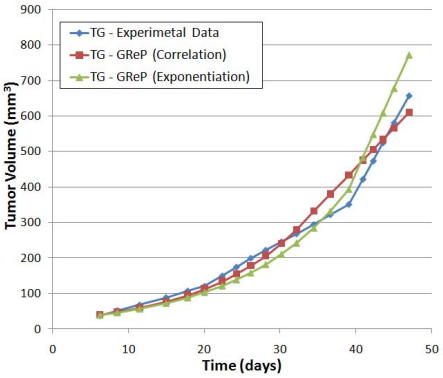

Fig. 4. Case IV: Tumor growth results from experimental data, and GREP model methods for MDA-MB-231 cell line with sub-cell line 4175

clinical experiments using breast cancer cell lines. Growth curves generated by GREP model, for the initial exponential phase of growth, closely match the pre-clinical data from the literature. These promising results show that it may be possible to build tools combining clinical information and genomic data to model cancerous tumor growth. As experiments progress, small discrepancies between the computed and experimental parameters get amplified for certain cases. We also observe that both methods of GREP are effective in determining tumor growth parameters. Therefore, exponentiation method is preferable when impact of individual genes on disease progression is known whereas correlation method can be chosen when genomic information including characterization of co-regulation between genes is available.

We plan to extend our model to drug absorbtion and efficacy dependent parameters. With PK/PD parameters, useful results for clinical support systems are expected.

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